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Diels–Alder Cycloadditions of 5-Hydroxy-2-pyrones: 2*H*-Pyran-2,5-diones and 5-(*tert*-Butyldimethylsilyloxy)-2-pyrones as Synthons

Wanqing Wu,[a] Shuzhong He,[a] Xiongfei Zhou,[a] and Chi-Sing Lee*[a]

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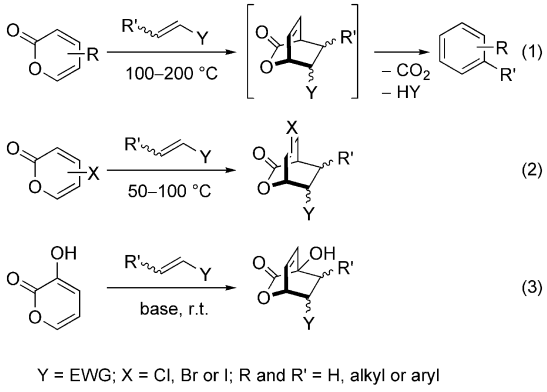
Diels–Alder (DA) cycloadditions of 5-hydroxy-2-pyrones based on the use of 2*H*-pyran-2,5-diones and 5-(*tert*-butyldimethylsilyloxy)-2-pyrones as synthons have been developed. Upon treatment either with a base or with a Lewis acid, 2*H*-pyran-2,5-diones equilibrated to 5-hydroxy-2-pyrones and underwent DA cycloaddition. The base-catalyzed protocol was optimized with *c*Hex_2NMe (0.1 equiv.) in *t*BuOH at room temperature, which gave the bicyclic cycloadducts in yields of up to 81 % (*endo*/*exo* = 6.2:1). The Lewis-acid-promoted protocol was optimized by conversion of 2*H*-pyran-2,5-diones into 5-(*tert*-butyldimethylsilyloxy)-2-pyrones and use of BF_3·OEt_2, which afforded the same DA products in yields of up to 90 % (*endo*/*exo* = 12:1).

Introduction

Diels–Alder (DA) cycloaddition of 2-pyrones has been developed into a useful method in organic synthesis.[1] In the early 1970s, DA cycloadditions of 2-pyrones were commonly carried out at high reaction temperatures (ca. 100–200 °C), due to their partially aromatic characters and low reactivities towards common dienophiles.[1,2] Under these forcing conditions, the bridged bicyclic lactone intermediates readily underwent decarboxylation to afford cyclohexadiene intermediates, which could further aromatize through loss of a hydrogen molecule or elimination to afford benzene systems [Equation (1) in Scheme 1].[1,3] Indeed, this methodology was widely utilized in the synthesis of highly functionalized aromatic compounds at that time.[1,4]

Because bridged bicyclic lactone intermediates are known as useful building blocks for natural product synthesis, various strategies for capturing these intermediates have been developed. Early studies showed that application of high pressures (14–20 kbar)[2,5] and/or employment of Lewis acids[6] for 2-pyrones with appropriate substitution on the 2-pyrone ring can successfully suppress the decarboxylation step, affording the bridged bicyclic adducts as the final products. Another popular approach is to introduce a halogen at the 3- and/or 5-position of the pyrone ring. Indeed, extensive studies on halogenated 2-pyrones have been carried out by the groups of Posner, Afarinkia, and Cho.[7] Various 3- and/or 5-halogenated 2-pyrones have been demonstrated to be very versatile and to be able to react both with electron-poor and with electron-rich dienophiles at reaction temperatures below 100 °C [Equation (2), Scheme 1], and the bridged bicyclic lactone adducts have been shown to be useful intermediates in natural product synthesis.[8] In 1995, Nakatani's group reported the first base-catalyzed DA cycloadditions of 3-hydroxy-2-pyrones for the initial preparation of bicyclic lactones at room temperature [Equation (3), Scheme 1][9] and further developed this mild reaction into an asymmetric version with the use of chiral acrylates and natural cinchona alkaloids.[10] Highly enantioselective DA reactions of 3-hydroxy-2-pyrones based on a new class of bifunctional organocatalysts were recently developed by Deng's group.[11]



Scheme 1. Various types of 2-pyrone DA cycloadditions.

Although DA cycloadditions of 3-hydroxy-2-pyrones have been studied quite extensively, no DA cycloadditions of 5-hydroxy-2-pyrones had been reported. Inspired by the pioneers' work, we decided to develop a new class of 2-pyrone DA cycloaddition with 5-hydroxy-2-pyrone as the

[a] Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Shenzhen Graduate School of Peking University, Shenzhen University Town,
Xili, Shenzhen 518055, Republic of China
Fax: +86-755-26032701
E-mail: lizc@szpku.edu.cn

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substrate to establish the tricyclic core of basiliolide B (Figure 1). In the course of this study, we have found that 2*H*-pyran-2,5-diones can be converted into 5-hydroxy-2-pyrones by treatment with catalytic amounts of base and undergo DA cycloaddition with acrylates at room temperature in a one-pot manner.[12] Here we disclose our full study of this new class of 2-pyrone DA cycloadditions, in which both the 2*H*-pyran-2,5-dione **1** and the 5-(*tert*-butyldimethylsilyloxy)-2-pyrone **2** can be utilized as synthons for 5-hydroxy-2-pyrones for DA cycloaddition (Scheme 2).

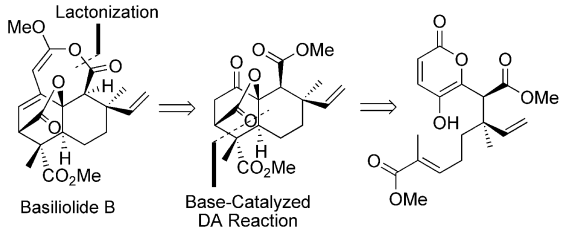
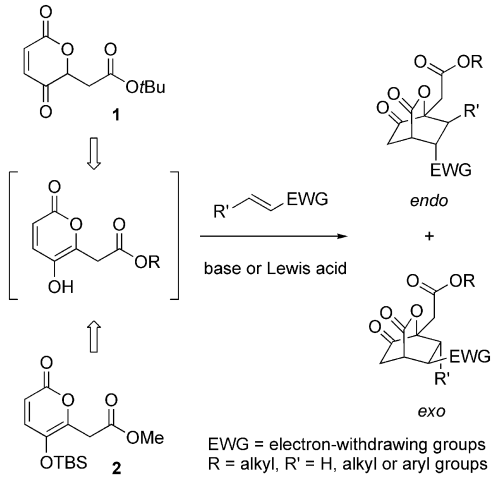


Figure 1. Base-catalyzed DA cycloaddition approach to the tricyclic core of basiliolide B.

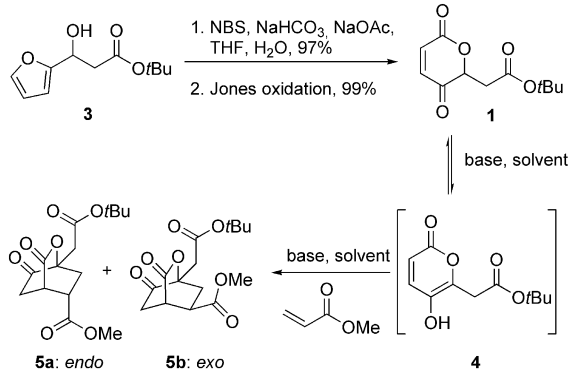


Scheme 2. DA cycloadditions of 5-hydroxy-2-pyrones with the 2*H*-pyran-2,5-dione **1** and the 5-(*tert*-butyldimethylsilyloxy)-2-pyrone **2** as the synthons.

Results and Discussion

Base-Catalyzed DA Cycloadditions of 2*H*-Pyran-2,5-diones

To investigate the utility of 2*H*-pyran-2,5-diones as synthons for 5-hydroxy-2-pyrones for DA cycloaddition, compound **1** was prepared from **3** by means of an Achmatowicz reaction[13] (NBS in aqueous THF) followed by Jones oxidation[14] (Scheme 3). With the reaction precursor to hand, DA cycloaddition between **1** and methyl acrylate under Nakatani's conditions was studied.[9] The reaction proceeded rapidly (2 h) in the presence of 1 equiv. of triethylamine in chloroform (Table 1, Entry 1), affording a 22% yield of the DA product with an *endo* selectivity of 4:1. The formation of the DA product can be explained in terms of equilibration of the 2*H*-pyran-2,5-dione **1** to the 5-hydroxy-2-pyrone **4** in the presence of triethylamine and subsequent [4+2] cycloaddition between **4** and methyl acrylate to give the DA product (**5**). An attempt employing catalytic amounts of triethylamine led only to trace amounts of **5** (Entry 2). After screening various solvents, including THF, CH_3CN, acetone, ethyl acetate, *i*PrOH, and *t*BuOH, we found that 0.2 equiv. of triethylamine in alcohol solvents provided the optimal conditions for the DA reactions. As shown in Table 1, the yield of **5** was improved to 70% in *i*PrOH as the solvent, but poor *endo* selectivity (2.5:1) resulted (Entry 7). Switching the solvent to *t*BuOH improved the *endo* selectivity to 5.3:1 but the yield was down to 55% (Entry 8). Use of different bases in *t*BuOH had only minor influences on the yields (58–68%) and *endo* selectivities (5.0:1 to 5.5:1) of the DA reactions (Entries 9–14). Use of the bulky base dicyclohexylmethylamine (*c*Hex_2NMe) gave the highest *endo* selectivity with a 62% yield of the DA products (Entry 12).



Scheme 3. 2*H*-Pyran-2,5-diones as synthons for 5-hydroxy-2-pyrones for DA cycloadditions.

Table 1. Base-catalyzed DA cycloaddition between the the 2*H*-pyran-2,5-dione **1** and methyl acrylate.[a]

Entry[a]	Base[b]/solvent	Yield[c] (%)	*endo*/*exo*[d]
1[e]	Et_3N[f]/$CHCl_3$	22	4.0:1
2	Et_3N/$CHCl_3$	trace	–
3	Et_3N/THF	trace	–
4	Et_3N/MeCN	30	6.0:1
5	Et_3N/EtOAc	25	3.0:1
6	Et_3N/acetone	45	4.0:1
7	Et_3N/*i*PrOH	70	2.5:1
8	Et_3N/*t*BuOH	55	5.5:1
9	Et_2NH/*t*BuOH	67	5.1:1
10	HMDS/*t*BuOH	58	5.2:1
11	DIPEA/*t*BuOH	61	5.1:1
12	*c*Hex_2NMe/*t*BuOH	62	5.5:1
13	*t*BuOK/*t*BuOH	61	5.0:1
14	pyrrolidine/*t*BuOH	68	5.2:1

[a] The general procedures were followed. [b] Base (0.2 equiv.) was used, reaction time: 7 d. [c] Isolated yields after silica gel flash column chromatography. [d] The *endo*/*exo* ratios were estimated by ^{1}H NMR (δ_{endo} = 3.21 ppm and δ_{exo} = 3.01 ppm). [e] Reaction time: 2 d. [f] Base (1.0 equiv.) was used.

The *exo* product (**5b**) was characterized unambiguously by analysis of its COSY and NOESY data (Figure 2, b). However, the stereochemistry of the *endo* product (**5a**)

could not be determined by NMR experiments, due to signal overlaps. Attempts to recrystallize **5a** from various solvent systems failed, so **5a** was converted into **6** with the aid of triethylamine in methanol. The crystals of **6** obtained by recrystallization from *n*-hexane/dichloromethane were found to be suitable for X-ray crystallography.[15] As shown in Figure 2 (a), the two methyl ester moieties of **6** were found to be *anti*, which is consistent with the stereochemistry of the expected *endo* product (**5a**).

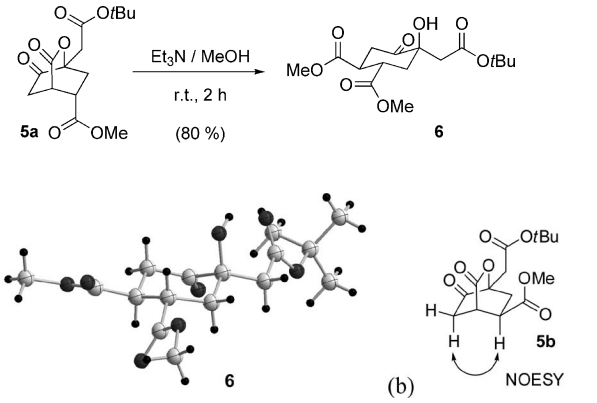


Figure 2. a) X-ray crystal structure of **6**; b) selected NOESY correlation in **5b**.

Because the results of the preliminary screening indicated that the alcohol solvents play an important role with regard to the yields and diastereoselectivities of the DA cycloaddition, the effects of *c*Hex_2NMe in a variety of alcohol solvents were investigated and the results are summarized in Table 2. Generally, the least sterically hindered alcohols gave the fastest reaction rates but the lowest *endo* selectivities, whereas the most hindered alcohol solvents gave the slowest reaction rates but with the highest *endo* selectivities. *c*Hex_2NMe in primary alcohol solvents afforded moderate yields of DA products with low *endo* selectivities (Entries 1–2). The highest *endo* selectivity was achieved with *c*Hex_2NMe in *tert*-amyl alcohol (*t*AmOH), but only a moderate yield of the DA products was obtained (Entry 6).

Table 2. Effect of alcohol solvents on DA cycloaddition between **1** and methyl acrylate.[a]

Entry[a]	Solvent	Time	Yield[b] (%)	*endo*/*exo*[c]
1	MeOH	3 d	52	2.0:1
2	*n*PrOH	4 d	56	2.0:1
3	*i*PrOH	4 d	65	2.7:1
4	*s*BuOH	6 d	40	4.0:1
5	*t*BuOH	7 d	62	5.5:1
6	*t*AmOH	7 d	53	8.0:1

[a] The general procedures were followed with *c*Hex_2NMe (0.2 equiv.). [b] Isolated yields after silica gel flash column chromatography. [c] The *endo*/*exo* ratios were estimated by ^{1}H NMR (δ_{endo} = 3.21 ppm and δ_{exo} = 3.01 ppm).

The base loading effects with the *c*Hex_2NMe/*t*BuOH system were also investigated, and the results are summarized in Table 3. High base loading generally resulted in a fast reaction rate but low *endo* selectivity. Although the DA reaction in the presence of 1 equiv. of base was complete in 1 d, a low yield and a low *endo* selectivity resulted (Entry 1). The highest *endo* selectivity was achieved with *c*Hex_2NMe (0.02 equiv.), but the reaction required 10 d with only an 18% yield of the DA products being isolated (Entry 6). Optimal conditions were found with *c*Hex_2NMe (0.1 equiv.), which gave a 58% yield of the DA products with *endo* selectivity equal to 8.5:1 (Entry 4). Increasing the reaction temperature to 50 °C under the same conditions led to a shorter reaction time (2 d), but a lower yield (50%) and a lower *endo* selectivity (*endo*/*exo* = 3.6:1) resulted (Entry 5).

Table 3. Effect of the base loading on DA reactions between **1** and methyl acrylate.[a]

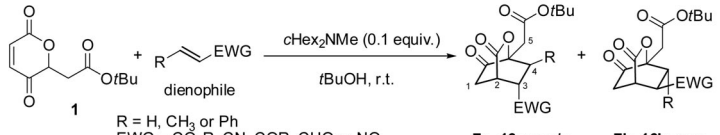
Entry[a]	Equiv.	Time	Yield[b] (%)	*endo*/*exo*[c]
1	1.0	1 d	40	2.5:1
2	0.5	3 d	45	4.4:1
3	0.2	7 d	62	5.5:1
4	0.1	7 d	58	8.5:1
5[d]	0.1	2 d	50	3.6:1
6	0.05	7 d	46	20:1
7	0.02	10 d	18	30:1

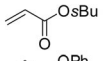
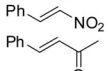
[a] The general procedures were followed with the indicated amount of *c*Hex_2NMe in *t*BuOH. [b] Isolated yields after silica gel flash column chromatography. [c] The *endo*/*exo* ratios were estimated by ^{1}H NMR (δ_{endo} = 3.21 ppm and δ_{exo} = 3.01 ppm). [d] Reaction temperature: 50 °C.

With the base-catalyzed DA cycloaddition conditions optimized, the scope of this reaction was studied with a variety of dienophiles. As shown in Table 4, the bulks of different alkyl acrylates did not show significant effects on the yields or the *endo* selectivities (Entries 1–3). Phenyl acrylate also gave similar results (Entry 4). The reactivity of acrylonitrile is much lower than those of alkyl acrylates, with only a 36% yield of the DA products being obtained after 15 d, with a low *endo* selectivity (Entry 5). On the other hand, the DA reaction of methyl vinyl ketone (MVK) proceeded rapidly (10 h) and gave an excellent yield (81%) with an *endo*/*exo* ratio of 6.2:1 (Entry 6). Both acrolein and crotonaldehyde led to unstable products, which decomposed upon purification (Entries 7 and 8). Attempts to oxidize the crude aldehydes to the corresponding acids with $NaClO_2$ also led to decomposition of the aldehydes. Of the disubstituted dienophiles, 2-nitrovinylbenzene was found to be the most reactive dienophile toward **1** under basic conditions (Entry 9). Interestingly, the DA reactions both of benzylideneacetone and of pent-3-en-2-one in the presence of *c*Hex_2NMe led to incomplete reactions. Switching the base to pyrrolidine led to complete reactions in 1–4 d with 49–52% yields (Entries 10–11). All the disubstituted dienophiles gave only the *exo* products (Entries 9–11). The structures of **14**–**16b** were characterized unambiguously by X-ray crystallography.[15,16] The *exo* selectivity is consistent with the results for the DA reactions of 3-hydroxy-2-pyrones reported by Deng's group.[11]

To study the mechanism of DA cycloadditions of 2*H*-pyran-2,5-diones, the 5-hydroxy-2-pyrone **4** was prepared by base- or acid-induced equilibration of the 2*H*-pyran-2,5-dione **1**. As shown in Table 5, the 2*H*-pyran-2,5-dione **1** was quite stable in $CDCl_3$ and no equilibration product (**4**) was

Table 4. Base-catalyzed DA cycloadditions between **1** and various dienophiles.[a]

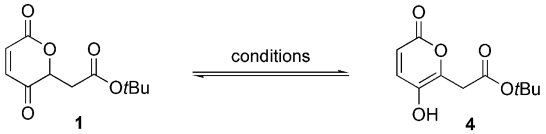


Entry	Dienophile	DA Products	Time	Yield[b] (%)	*endo*/*exo*[c]
1		**5a**,**b**	7 d	58	8.5:1
2		**7a**,**b**	7 d	63	8.0:1
3		**8a**,**b**	7 d	61	8.2:1
4		**9a**,**b**	4 d	60	7.8:1
5		**10a**,**b**	15 d	32	3.6:1
6		**11a**,**b**	10 h	81	6.2:1
7		**12a**,**b**	–	–	–
8		**13a**,**b**	–	–	–
9		**14a**,**b**	10 h	43	*exo* only[e]
10[d]		**15a**,**b**	1 d	49	*exo* only
11[d]		**16a**,**b**	4 d	52	*exo* only

[a] The general procedures were followed with *c*Hex$_2$NMe (0.1 equiv.) in *t*BuOH. [b] Isolated yields after silica gel flash column chromatography. [c] The *endo*/*exo* ratios were estimated by ^{1}H NMR (δ_{endo} = 3.21 ppm and δ_{exo} 3.01 = ppm). The *endo*/*exo* ratio in **11** dropped to 2:1 after 5 d stirring; **5**–**10** and **14**–**16** are stable under the reaction conditions. [d] Pyrrolidine was used as the base. [e] Yield 48%, *endo*/*exo* = 1:5.4 when pyrrolidine was used as the base.

observed in $CDCl_3$ even after stirring at room temperature for 7 d (Entry 1). Addition of catalytic amounts of acetic acid in CH_2Cl_2 or *t*BuOH induced the equilibration and afforded a 1.8:1 mixture and a 1.5:1 mixture, respectively (Entries 2 and 3). Employment of base catalysts such as *c*Hex$_2$NMe allowed complete equilibration of the 2*H*-pyran-2,5-dione **1** to the 5-hydroxy-2-pyrone **4** in 20 h (Entry 4).

Table 5. Equilibration of the 2*H*-pyran-2,5-dione **1** to the 5-hydroxy-2-pyrone **4**.

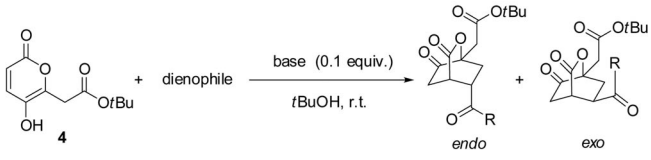


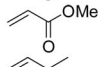
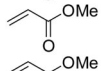
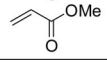
Entry	Conditions[a]	Time	**1**/**4**[b]	Yield[c] (%)
1	$CDCl_3$	48 h	**1** only	–
2	CH_3CO_2H/CH_2Cl_2	48 h	1.8:1	–
3	CH_3CO_2H/*t*BuOH	48 h	1.5:1	–
4	*c*Hex$_2$NMe/*t*BuOH	20 h	**4** only	95

[a] Acetic acid or *c*Hex$_2$NMe (0.1 equiv.) was used. [b] The **1**/**4** ratio was estimated by ^{1}H NMR spectroscopy. [c] ^{1}H NMR of the crude product (**4**) indicated satisfactory purity for DA cycloaddition without further purification.

With the 5-hydroxy-2-pyrone **4** prepared, its DA cycloaddition with methyl acrylate and MVK was first studied in the absence of any base. As expected, only trace amounts

Table 6. DA cycloaddition of the 5-hydroxy-2-pyrone **4**.[a]



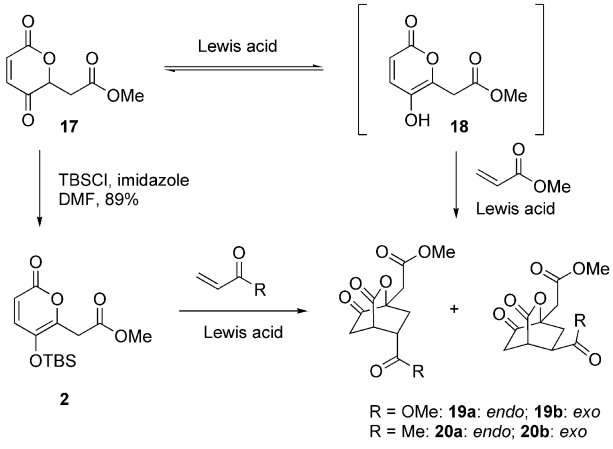
Entry	Base	Diene	Dienophile	Time	Yield[b] (%)	*endo*/*exo*[c]
1	–	**4**		14 d	trace	–
2	–	**4**		14 d	trace	–
3	*c*Hex$_2$NMe	**1**		10 h	81	6.2:1
4	*c*Hex$_2$NMe	**4**		19 h	68	2.3:1
5	*c*Hex$_2$NMe	**1**		7 d	58	8.5:1
6	*c*Hex$_2$NMe	**4**		9 d	56	7.0:1

[a] The general procedures were followed. [b] Isolated yields after silica gel flash column chromatography. [c] The *endo*/*exo* ratios were estimated by ^{1}H NMR (δ_{endo} = 3.21 and δ_{exo} = 3.01 ppm).

of the DA products were observed after the systems had been stirred at room temperature for 14 d (Table 6, Entries 1 and 2). Surprisingly, employment of the optimal conditions for the DA cycloaddition of **4** with methyl acrylate or MVK led to longer reaction times with lower yields and lower *endo* selectivities (Entries 3–6). The significant drop in the *endo* selectivity with MVK as the dienophile (Entry 4) may be due to equilibration of the *endo* product to the *exo* product over the longer reaction time.

Lewis-Acid-Promoted DA Cycloadditions of 5-(*tert*-Butyldimethylsilyloxy)-2-pyrones

Because Lewis acids have been demonstrated to be effective promoters for DA cycloadditions of certain substituted pyrone derivatives,[6] we decided to investigate the utilities of Lewis acids in the DA cycloadditions of 2*H*-pyran-2,5-diones. Because of the lability of the *tert*-butyl ester of **1** under acidic conditions, the 2*H*-pyran-2,5-dione **17** was prepared from methyl acetate and 2-furaldehyde by procedures similar to those used for the synthesis of **1**.[17] The 2*H*-pyran-2,5-dione **17** was expected to equilibrate to the 5-hydroxy-2-pyrone **18** upon treatment with a Lewis acid, analogously to the situation in the base-catalyzed DA cycloadditions, and was able to undergo DA cycloaddition with methyl acrylate in a one-pot manner (Scheme 4). An alternative approach would be conversion of the 2*H*-pyran-2,5-dione **17** into the 5-(*tert*-butyldimethylsilyloxy)-2-pyrone **2** as a synthon for **18** for the Lewis-acid-promoted DA cycloaddition. Compound **2** was readily prepared from **17** by treatment with TBSCl and imidazole in DMF.



Scheme 4. Compounds **2** and **17** as synthons for the 5-hydroxy-2-pyrone **18** for DA cycloadditions.

The DA cycloadditions of both **2** and **17** with methyl acrylate in the presence of $BF_3{\cdot}OEt_2$ and $AlCl_3$ were studied. Surprisingly, the DA cycloadditions of **2** and **17** both proceeded very slowly in CH_2Cl_2 at room temperature even with 3 equiv. of the Lewis acids. The slow reactions could be the result of the presence of multiple carbonyl moieties in the substrates and products. Compound **2** was found to be quite stable towards the Lewis acids and significant amounts of the substrates were recovered after 10 d stirring at room temperature. Lewis-acid-promoted DA cycloadditions of **17** were generally less efficient than those of **2**. $BF_3{\cdot}OEt_2$ gave 60 and 49% yields of the DA products from **2** and **17**, respectively (Table 7, Entries 1–2). Switching the Lewis acid to $AlCl_3$ led to lower yields (Entries 3–4). DA cycloaddition of **2** also provided better *endo* selectivity than that of **17**. The structures of the *endo* (**19a**) and the *exo* (**19b**) products were characterized unambiguously by X-ray crystallography and NOESY, respectively (Figure 3).[15]

Table 7. Lewis-acid-promoted DA cycloadditions between **2** or **17** and methyl acrylate.[a]

Entry	Diene	Lewis acid	Yield[b] (%)	*endo*/*exo*[c]
1	**17**	$BF_3{\cdot}OEt_2$	49 (49)	3.9:1
2	**2**	$BF_3{\cdot}OEt_2$	60 (72)	7.7:1
3	**17**	$AlCl_3$	25 (25)	3.6:1
4	**2**	$AlCl_3$	40 (48)	10:1
5	**2**	$SnCl_4$	36 (61)	*endo* only
6	**2**	$TiCl_4$	28 (28)	*endo* only
7	**2**	$InCl_3$	30 (43)	20:1
8	**2**	$AgSbF_6$	18 (53)	7.0:1
9	**2**	$Yb(OTf)_3$	trace	–
10	**2**	ZnF_2	trace	–
11	**2**	MgF_2	22 (37)	6.2:1

[a] The general procedures were followed and reaction time: 10 d. [b] Isolated yields after silica gel flash column chromatography. Yields based on recovered starting materials are in parentheses. [c] The *endo*/*exo* ratios were estimated by ^1H NMR (δ_{endo} = 3.24 and δ_{exo} = 3.03 ppm).

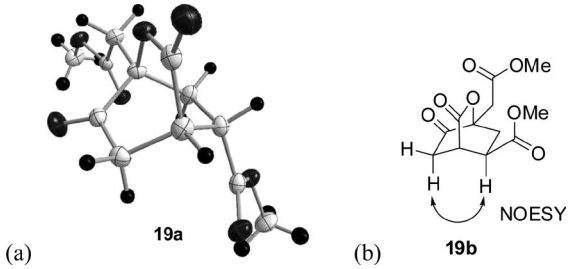


Figure 3. a) X-ray crystal structure of **19a**; b) selected NOESY correlation in **19b**.

Because the Lewis-acid-promoted DA cycloadditions of **2** had provided better results than those of **17**, DA cycloadditions between **2** and methyl acrylate in the presence of various Lewis acids were investigated. As shown in Table 7, $SnCl_4$ and $TiCl_4$ provided 36 and 28% yields, respectively, with only the *endo* product (Entries 5 and 6). $InCl_3$ also gave very high *endo* selectivity, with a 30% yield (Entry 7). $AgSBF_6$ afforded a poor yield and *endo* selectivity (Entry 8). $Yb(OTf)_3$ and ZnF_2 gave trace amounts of the DA products (Entries 9 and 10), whereas MgF_2 afforded only a 22% yield with an *endo* selectivity of 6.2:1 (Entry 11). The optimal yield of the DA products was obtained with $BF_3{\cdot}OEt_2$, which also provided a good *endo* selectivity (7.7:1). $SnCl_4$, $TiCl_4$, and $InCl_3$ provided excellent *endo* selectivities but with modest yields. Although the degrees of conversion and the yields of the Lewis-acid-promoted DA

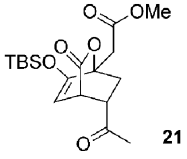
cycloadditions are quite low, the diastereoselectivities are generally higher than those from the base-catalyzed DA cycloadditions.

DA cycloadditions of **2** and **17** with the more reactive dienophile MVK were also studied. In the presence of $BF_3{\cdot}OEt_2$, its DA cycloaddition with **17** also went very slowly at room temperature and gave only a 40% yield of the DA products with modest *endo* selectivity (Entry 1, Table 8). On the other hand, the DA cycloaddition between **2** and MVK went to completion in 7 h at room temperature and afforded the DA products in very good yield (90%) with good *endo* selectivity (*endo*/*exo* = 12:1, Entry 2). This encouraging result prompted us to study the effect of the Lewis acid loading on the DA cycloadditions between **2** and MVK. As shown in Table 8, reducing the amount of $BF_3{\cdot}OEt_2$ to 0.5 and 0.2 equiv. led to much slower reactions (7 and 15 d, respectively) with moderate yields (62 and 51%, respectively) and excellent *endo* selectivity of the DA products (Entry 3 and 4). An attempt to speed up the DA cycloaddition by raising the reaction temperature (50 °C) in a sealed tube reduced the reaction time to 10 d with a 45% yield of the DA product and the same *endo* selectivity (Entry 5). Addition of water just halted the DA cycloaddition (Entry 6). A variety of Lewis acids were investigated and the results are summarized in Table 8. $AlCl_3$ gave a poor yield with only the *endo* product (Entry 7). $InCl_3$ and $In(OTf)_3$ afforded 44 and 62% yields, respectively, of the DA products with good *endo* selectivities (Entries 8 and 9). $AgSbF_6$ also gave a reasonable reaction rate and yield with modest *endo* selectivity (Entry 10). Use of $Zn(OTf)_2$ resulted in a very slow reaction (12 d) and afforded a 52% yield with excellent *endo* selectivity (Entry 11). The Lewis-acid-promoted DA cycloaddition between **2** and the more active dienophile MVK was optimized by use of a stoichiometric amount of $BF_3{\cdot}OEt_2$, with yields up to 90% and good *endo* selectivity (*endo*/*exo* = 12:1). Without a Lewis acid, DA cycloaddition between compound **2** and MVK required 1 d in toluene at 80 °C for completion and gave a 73% yield of **21** exclusively in the form of the *endo* product (Entry 12).[18] Although the thermal DA cycloaddition of **2** is less efficient than the Lewis-acid-promoted DA cyclizations, the silyl enol ether moiety in **21** could provide a useful handle for the development of cascade cyclization reactions.

Table 8. Lewis-acid-promoted DA cycloadditions between **2** or **17** and MVK.[a]

Entry	Diene	Lewis acid (equiv.)	Time	Yield[b] (%)	*endo*/*exo*[c]
1	**17**	$BF_3{\cdot}OEt_2$ (1.2)	8 d	40	5.0:1
2	**2**	$BF_3{\cdot}OEt_2$ (1.2)	7 h	90	12:1
3	**2**	$BF_3{\cdot}OEt_2$ (0.5)	8 d	62	13:1
4	**2**	$BF_3{\cdot}OEt_2$ (0.2)	15 d	51	*endo* only
5	**2**	$BF_3{\cdot}OEt_2$ (0.2) [d]	10 d	45	*endo* only
6	**2**	$BF_3{\cdot}OEt_2$ (0.2) [e]	14 d	trace	–
7	**2**	$AlCl_3$ (1.2)	1 d	15	*endo* only
8	**2**	$InCl_3$ (1.2)	36 h	44	16:1
9	**2**	$In(OTf)_3$ (1.2)	36 h	62	12:1
10	**2**	$AgSbF_6$ (3.0)	3 d	46	5.0:1
11	**2**	$Zn(OTf)_2$ (5.0)	12 d	52	*endo* only
12[f]	**2**	–	1 d	73[g]	*endo* only

[a] The general procedures were followed. [b] Isolated yields (%) after silica gel flash column chromatography. [c] The *endo*/*exo* ratios were estimated by ^1H NMR (δ_{endo} = 3.30 and δ_{exo} = 3.09 ppm). [d] Reaction temperature: 50 °C in a sealed tube in $ClCH_2CH_2Cl$ as solvent. [e] Solvent = CH_2Cl_2/H_2O (10:1). [f] Reaction temperature: 80 °C in a sealed tube with toluene as solvent. [g] DA product **21** was isolated.



21

Conclusions

In summary, Diels–Alder cycloadditions of 5-hydroxy-2-pyrones have been developed by use of 2*H*-pyran-2,5-diones and 5-(*tert*-butyldimethylsilyloxy)-2-pyrones as synthons. Upon treatment with catalytic amounts of base, the 2*H*-pyran-2,5-diones equilibrated to the 5-hydroxy-2-pyrones and underwent DA cycloadditions with a variety of dienophiles. The conditions were optimized by use of cHex$_2$NMe (0.1 equiv.) in tBuOH, which gave the bicyclic cycloadducts in an 81% yield with an *endo*/*exo* ratio of 6.2:1. In the presence of Lewis acids, however, this equilibration/DA cycloaddition protocol resulted in poor yields. The problem was solved by conversion of the 2*H*-pyran-2,5-diones into 5-(*tert*-butyldimethylsilyloxy)-2-pyrones, which underwent Lewis-acid-promoted DA cycloadditions and afforded excellent results (90% yield, *endo*/*exo* = 12:1). Although the DA cycloaddition of 5-(*tert*-butyldimethylsilyloxy)-2-pyrones required stoichiometric amounts of Lewis acids, this reaction provided the DA products with better yields and *endo* selectivities than those from the base-catalyzed versions. The versatility of this new class of 2-pyrone DA cycloaddition could provide a useful strategy in organic synthesis. Indeed, the utility of this new method in natural product synthesis is being actively explored in our group.

Experimental Section

General: All air- and water-sensitive reactions were carried out under nitrogen in dry solvents under anhydrous conditions, unless otherwise noted. All the chemicals were purchased commercially and used without further purification. Anhydrous THF was distilled from sodium-benzophenone, and dichloromethane was distilled from calcium hydride. Yields refer to chromatographic purification unless otherwise stated.

Reactions were monitored by thin-layer chromatography (TLC) carried out on Tsingdao silica gel plates (60F-254, 0.25 mm) that were analyzed by staining with $KMnO_4$ [H_2O (200 mL), $KMnO_4$ (1.5 g), K_2CO_3 (10 g), aqueous NaOH (10%,1.25 mL)]. Tsingdao silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography.

Melting points were uncorrected and determined with a micro-melting point meter (Beijing Tech Instrument Co. LTD, X-6). NMR spectra were recorded either with a Bruker Advance 300 (^1H:

300 MHz, ^{13}C: 75.5 MHz) instrument or with a Bruker Advance 500 (^1H: 500 MHz, ^{13}C: 125.8 MHz). The following abbreviations are used to denote the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br. = broad. High-resolution mass spectra were obtained with an Applied Biosystems (ABI) Q-Star Elite MALDI-TOF mass spectrometer. Crystallographic data were obtained with an Oxford diffraction single-crystal X-ray diffractometer (Gemini S Ultra).

General Procedure for the Base-Catalyzed Diels–Alder Cycloaddition of *tert*-Butyl 2-(3,6-Dioxo-3,6-dihydro-2*H*-pyran-2-yl)acetate (1): *c*Hex_2NMe (0.01 mmol) was added to a stirred solution of **1** (0.1 mmol) and the appropriate dienophile (0.5 mmol) in *t*BuOH (1.5 mL). The resulting mixture was stirred at room temperature and monitored by TLC until the starting material had been consumed. The reaction was worked up by addition of a saturated aqueous NH_4Cl solution and the aqueous layer was extracted with diethyl ether (×3). The combined extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated. The residue was then purified by silica gel flash column chromatography to give the DA products.

Methyl 1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]-octane-8-*endo*-carboxylate (5a) and Methyl 1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]octane-8-*exo*-carboxylate (5b): Yield 18 mg, 58%, *endo*/*exo* = 8.5:1. Compound **5a** (white solid): m.p. 91–92 °C, R_f = 0.66 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (125 MHz, $CDCl_3$, 25 °C): δ = 3.76 (s, 3 H, OCH_3), 3.38 (q, J = 3.0 Hz, 1 H, 2-H), 3.21 (m, 1 H, 3-H), 2.83 (d, J = 16.5 Hz, 1 H, 5-H), 2.67 (m, 5 H, 5-H, 1-H, 4-H), 1.44 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 201.3, 171.3, 170.9, 167.4, 84.7, 81.9, 53.0, 39.5, 37.6, 37.6, 35.1, 31.0, 28.2 ppm. HRMS (ESI) calcd. for $C_{15}H_{20}O_7Na$ [M + Na]$^+$ 335.1107; found 335.1104. Compound **5b** (yellow oil): R_f = 0.51 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (125 MHz, $CDCl_3$, 25 °C): δ = 3.77 (s, 3 H, OCH_3), 3.36 (dd, J = 5.0, 3.0 Hz, 1 H, 2-H), 3.01 (ddd, J = 11.0, 6.5, 1.2 Hz, 1 H, 3-H), 2.78 (m, 4 H, 5-H, 1-H, 4-H), 2.62 (dd, J = 19.0, 2.5 Hz, 1 H, 1-H), 2.51 (dd, J = 15.0, 10.5 Hz, 1 H, 4-H), 1.46 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 202.1, 171.7, 169.9, 167.5, 84.1, 82.0, 53.1, 40.6, 40.2, 38.4, 37.9, 31.5, 28.2 ppm. HRMS (ESI) calcd. for $C_{15}H_{20}O_7Na$ [M + Na]$^+$ 335.1107; found 335.1105.

Ethyl 1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]-octane-8-*endo*-carboxylate (7a) and Ethyl 1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]octane-8-*exo*-carboxylate (7b): Yield 21 mg, 63%, *endo*/*exo* = 8.0:1. Compound **7a** (yellow oil): R_f = 0.69 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.22 (dq, J = 7.1, 1.6 Hz, 2 H, OCH_2CH_3), 3.40 (dt, J = 5.7, 2.8 Hz, 1 H, 2-H), 3.19 (m, 1 H, 3-H), 2.85 (d, J = 16.5 Hz, 1 H, 5-H), 2.68 (m, 5 H, 5-H, 1-H, 4-H), 1.46 (s, 9 H, *t*Bu), 1.30 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 201.4, 171.0, 170.8, 167.4, 84.8, 81.9, 62.2, 39.6, 37.7, 37.7, 35.1, 31.0, 28.2, 14.3 ppm. IR (KBr): $\tilde{\nu}$ = 2980, 2935, 2874, 1776, 1751, 1733, 1455, 1369, 1256, 1208, 1161, 1039, 988 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{22}O_7Na$ [M + Na]$^+$ 349.1263; found 349.1261. Compound **7b** (yellow oil): R_f = 0.58 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.22 (m, 2 H, OCH_2CH_3), 3.35 (dt, J = 4.8, 2.7 Hz, 1 H, 2-H), 2.99 (ddd, J = 10.8, 6.8, 1.9 Hz, 1 H, 3-H), 2.77 (m, 4 H, 5-H, 1-H, 4-H), 2.62 (dd, J = 19.0, 2.7 Hz, 1 H, 1-H), 2.50 (dd, J = 15.2, 10.8 Hz, 1 H, 4-H), 1.46 (s, 9 H, *t*Bu), 1.30 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 202.2, 171.3, 169.9, 167.5, 84.1, 82.0, 62.3, 40.7, 40.3, 38.4, 37.9, 31.4, 28.2, 14.2 ppm. IR (KBr): $\tilde{\nu}$ = 2980, 2933, 2874, 2843, 1775, 1733, 1456, 1369, 1157, 1034, 975 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{22}O_7Na$ [M + Na]$^+$ 349.1263; found 349.1265.

Isobutyl 1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]-octane-8-*endo*-carboxylate (8a) and Isobutyl 1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]octane-8-*exo*-carboxylate (8b): Yield 22 mg, 61%, *endo*/*exo* = 8.2:1. Compound **8a** (white solid): m.p. 79–80 °C, R_f = 0.51 (silica gel, hexanes/ethyl acetate 3:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.95 [m, 2 H, $OCH_2CH(CH_3)_2$], 3.40 (dt, J = 5.7, 2.8 Hz, 1 H, 2-H), 3.23 (m, 1 H, 3-H), 2.86 (d, J = 16.4 Hz, 1 H, 5-H), 2.68 (m, 5 H, 5-H, 1-H, 4-H), 1.95 [m, 1 H, $OCH_2CH(CH_3)_2$], 1.46 (s, 9 H, *t*Bu), 0.94 [d, J = 6.7 Hz, 6 H, $OCH_2CH(CH_3)_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 201.3, 171.0, 170.9, 167.4, 84.8, 81.9, 72.3, 39.7, 37.8, 37.7, 35.1, 31.0, 28.2, 27.9, 19.1 ppm. IR (KBr): $\tilde{\nu}$ = 2981, 2966, 2932, 2875, 1777, 1752, 1736, 1451, 1366, 1275, 1208, 1193, 1149, 1046, 938 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{26}O_7Na$ [M + Na]$^+$ 377.1576; found 377.1575. Compound **8b** (white solid): m.p. 37–38 °C, R_f = 0.36 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.96 [m, 2 H, $OCH_2CH(CH_3)_2$], 3.36 (dt, J = 4.8, 2.8 Hz, 1 H, 2-H), 3.02 (ddd, J = 10.8, 6.8, 1.8 Hz, 1 H, 3-H), 2.76 (m, 4 H, 5-H, 1-H, 4-H), 2.63 (dd, J = 19.0, 2.8 Hz, 1 H, 1-H), 2.51 (dd, J = 15.2, 10.8 Hz, 1 H, 4-H), 1.96 [m, 1 H, $OCH_2CH(CH_3)_2$], 1.46 (s, 9 H, *t*Bu), 0.95 [d, J = 6.7 Hz, 6 H, $OCH_2CH(CH_3)_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 202.2, 171.3, 169.8, 167.5, 84.1, 82.0, 72.3, 40.8, 40.3, 38.4, 37.9, 31.5, 28.2, 27.9, 19.1 ppm. IR (KBr): $\tilde{\nu}$ = 2974, 2955, 2935, 2873, 1767, 1736, 1696, 1450, 1367, 1261, 1209, 1142, 1038, 942 cm^{-1}. HRMS (ESI) calcd. for $C_{18}H_{26}O_7Na$ [M + Na]$^+$ 377.1576; found 377.1575.

Phenyl 1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]-octane-8-*endo*-carboxylate (9a) and Phenyl 1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]octane-8-*exo*-carboxylate (9b): Yield 22 mg, 60%, *endo*/*exo* = 7.8:1. Compound **9a** (white solid): m.p. 118–119 °C, R_f = 0.53 (silica gel, hexanes/ethyl acetate 3:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.41 (m, 2 H, Ph), 7.28 (m, 1 H, Ph), 7.08 (m, 2 H, Ph), 3.59 (dt, J = 6.0, 3.0 Hz, 1 H, 2-H), 3.49 (m, 1 H, 3-H), 2.81 (m, 6 H, 1-H, 4-H, 5-H), 1.47 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 201.0, 170.6, 169.6, 167.4, 150.4, 129.8, 126.7, 121.2, 84.8, 82.0, 39.6, 38.0, 37.7, 35.1, 31.0, 28.2 ppm. IR (KBr): $\tilde{\nu}$ = 3010, 2983, 2966, 2930, 1771, 1746, 1494, 1378, 1376, 1197, 1175, 1148 cm^{-1}. HRMS (ESI) calcd. for $C_{20}H_{22}O_7Na$ [M + Na]$^+$ 397.1263; found 397.1262. Compound **9b** (light yellow oil): R_f = 0.34 (silica gel, hexanes/ethyl acetate 3:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.40 (m, 2 H, Ph), 7.27 (m, 1 H, Ph), 7.10 (m, 2 H, Ph), 3.57 (dt, J = 5.0, 2.5 Hz, 1 H, 2-H), 3.28 (ddd, J = 10.5, 6.5, 2.0 Hz, 1 H, 3-H), 2.86 (m, 4 H, 1-H, 4-H, 5-H), 2.72 (dd, J = 19.0, 2.5 Hz, 1 H, 1-H), 2.63 (dd, J = 15.5, 10.5 Hz, 1 H, 4-H), 1.47 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 201.9, 169.9, 169.7, 167.5, 150.5, 129.8, 126.6, 121.3, 84.1, 82.1, 40.7, 40.5, 38.3, 37.9 31.2, 28.2 ppm. IR (KBr): $\tilde{\nu}$ = 2962, 2925, 2852, 1781, 1753, 1730, 1369, 1193, 1164, 1027 cm^{-1}. HRMS (ESI) calcd. for $C_{20}H_{22}O_7Na$ [M + Na]$^+$ 397.1263; found 397.1264.

1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]octane-8-*endo*-carbonitrile (10a) and 1-(2-*tert*-Butoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]octane-8-*exo*-carbonitrile (10b): Yield 9 mg, 32%, *endo*/*exo* = 3.6:1. Compound **10a** (white solid): m.p. 142–143 °C, R_f = 0.53 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.43 (m, 1 H, 3-H), 3.33 (dt, J = 5.8, 3.0 Hz, 1 H, 2-H), 3.10 (dd, J = 19.6, 2.5 Hz, 1 H, 1-H), 2.98 (dd, J = 15.5, 11.5 Hz, 1 H, 4-H), 2.86 (dt, J = 19.6, 2.4 Hz, 1 H, 1-H), 2.78 (dt, J = 33.1, 16.6 Hz, 2 H, 5-H), 2.53 (dd, J = 15.5,

4.3 Hz, 1 H, 4-H), 1.47 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 199.3, 168.6, 167.1, 117.8, 83.9, 82.4, 39.2, 37.2, 35.4, 32.3, 28.2, 24.5 ppm. IR (KBr): $\tilde{\nu}$ = 2982, 2932, 2843, 2244, 1773, 1757, 1731, 1369, 1238, 1158, 1110, 1042, 988 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{18}NO_5$ [M + H]$^+$ 280.1184; found 280.1185. Compound **10b** (yellow oil): R_f = 0.50 (silica gel, hexanes/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.38 (dt, *J* = 5.0, 2.7 Hz, 1 H, 2-H), 3.21 (ddd, *J* = 10.8, 6.6, 2.0 Hz, 1 H, 3-H), 2.86 (m, 2 H, 1-H, 4-H), 2.80 (d, *J* = 2.9 Hz, 1 H, 5-H), 2.69 (dd, *J* = 15.3, 6.5 Hz, 1 H, 1-H), 2.66 (dd, *J* = 19.3, 2.7 Hz, 1 H, 4-H), 1.47 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 199.7, 167.7, 167.2, 118.4, 83.7, 82.5, 40.5, 38.0, 37.5, 33.0, 28.2, 25.8 ppm. IR (KBr): $\tilde{\nu}$ = 3064, 2959, 2924, 2850, 2235, 1782, 1755, 1731, 1631, 1452, 1369, 1265, 1155, 1023, 738 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{18}NO_5$ [M + H]$^+$ 280.1186; found 280.1185.

***tert*-Butyl 2-(8-*endo*-Acetyl-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl)-acetate (11a) and *tert*-Butyl 2-(8-*exo*-Acetyl-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl)acetate (11b):** Yield 24 mg, 81%, *endo*/*exo* = 6.2:1. Compound **11a** (white solid): m.p. 87–88 °C; R_f = 0.66 (silica gel, hexanes/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.36 (dt, *J* = 5.5, 2.7 Hz, 1 H, 2-H), 3.28 (m, 1 H, 3-H), 2.84 (d, *J* = 16.5 Hz, 1 H, 5-H), 2.71 (d, *J* = 16.5 Hz, 1 H, 5-H), 2.59 (m, 4 H, 1-H, 4-H), 2.26 (s, 3 H, $COCH_3$), 1.45 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 204.2, 200.8, 171.0, 167.5, 85.1, 81.8, 44.8, 39.0, 37.7, 34.4, 29.6, 28.6, 28.2 ppm. IR (KBr): $\tilde{\nu}$ = 3006, 2982, 2934, 2866, 1777, 1752, 1730, 1719, 1369, 1205, 1261, 1166, 1143, 1044, 971 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{20}O_6Na$ [M + Na]$^+$ 319.1157; found 319.1161. Compound **11b** (yellow oil): R_f = 0.50 (silica gel, hexanes/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.33 (dt, *J* = 4.7, 2.8 Hz, 1 H, 2-H), 3.07 (ddd, *J* = 10.7, 6.9, 1.7 Hz, 1 H, 3-H), 2.80 (m, 3 H, 5-H, 1-H), 2.71 (dd, *J* = 15.1, 6.9 Hz, 1 H, 4-H), 2.64 (dd, *J* = 19.0, 2.8 Hz, 1 H, 1-H), 2.42 (dd, *J* = 15.1, 10.7 Hz, 1 H, 4-H), 2.29 (s, 3 H, OCH_3), 1.47 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 204.3, 202.3, 169.8, 167.6, 84.1, 82.0, 47.9, 39.5, 38.4, 37.9, 30.1, 28.3, 28.2 ppm. IR (KBr): $\tilde{\nu}$ = 2978, 2917, 2843, 1770, 1750, 1728, 1717, 1638, 1257, 1157, 1104, 1032 cm^{-1}. HRMS (ESI) calcd. for $C_{15}H_{20}O_6Na$ [M + Na]$^+$ 319.1157; found 319.1162.

***tert*-Butyl 2-(8-*exo*-Nitro-3,6-dioxo-7-*endo*-phenyl-2-oxabicyclo-[2.2.2]octan-1-yl)acetate (14b):** Yield 16 mg, 43%, pale yellow solid, m.p. 190–191 °C; R_f = 0.30 (silica gel, hexanes/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.39 (m, 3 H, Ph), 7.06 (m, 2 H, Ph), 5.10 (dd, *J* = 7.0, 1.8 Hz, 1 H, 3-H), 4.73 (d, *J* = 7.0 Hz, 1 H, 4-H), 3.75 (d, *J* = 2.1 Hz, 1 H, 2-H), 3.06 (dd, *J* = 19.5, 3.2 Hz, 1 H, 1-H), 2.92 (dd, *J* = 19.5, 2.7 Hz, 1 H, 1-H), 2.64 (d, *J* = 17.2 Hz, 1 H, 5-H), 2.37 (d, *J* = 17.2 Hz, 1 H, 5-H), 1.43 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 199.0, 166.9, 166.8, 133.8, 129.8, 129.5, 128.7, 87.6, 86.6, 82.4, 51.0, 41.1, 36.5, 35.3, 28.2 ppm. IR (KBr): $\tilde{\nu}$ = 3068, 2982, 2940, 2919, 1779, 1753, 1732, 1458, 1379, 1368, 1246, 1232, 1103, 1022, 707 cm^{-1}. HRMS (ESI) calcd. for $C_{19}H_{22}NO_7$ [M + H]$^+$ 376.1396; found 376.1411.

***tert*-Butyl 2-(8-*exo*-Acetyl-3,6-dioxo-7-*endo*-phenyl-2-oxabicyclo-[2.2.2]octan-1-yl)acetate (15b):** Yield 18 mg, 49%, pale yellow solid, m.p. 151–152 °C; R_f = 0.43 (silica gel, hexanes/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.34 (m, 3 H, Ph), 7.11 (m, 2 H, Ph), 4.18 (d, *J* = 8.3 Hz, 1 H, 4-H), 3.41 (dt, *J* = 4.4, 2.8 Hz, 1 H, 2-H), 3.19 (dd, *J* = 1.3, 8.3 Hz, 1 H, 3-H), 2.98 (dd, *J* = 19.2, 2.9 Hz, 1 H, 1-H), 2.86 (dd, *J* = 19.2, 2.9 Hz, 1 H, 1-H), 2.58 (d, *J* = 17.0 Hz, 1 H, 5-H), 2.37 (d, *J* = 17.0 Hz, 1 H, 5-H), 2.12 (s, 3 H, $COCH_3$), 1.43 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 204.0, 201.8, 169.9, 167.2, 136.2, 129.5, 128.9, 128.8, 86.9, 81.9, 56.0, 48.7, 39.1, 38.6, 36.0, 28.9, 28.2 ppm. IR (KBr): $\tilde{\nu}$ = 3006, 2979, 2948, 2928, 1773, 1750, 1725, 1368, 1144, 1110, 1020, 709 cm^{-1}. HRMS (ESI) calcd. for $C_{21}H_{24}O_6Na$ [M + Na]$^+$ 395.1470; found 395.1466.

***tert*-Butyl 2-(8-*exo*-Acetyl-3,6-dioxo-7-*endo*-methyl-2-oxabicyclo-[2.2.2]octan-1-yl)acetate (16b):** Yield 16 mg, 52%, white solid, m.p. 165–166 °C; R_f = 0.33 (silica gel, hexanes/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.25 (dt, *J* = 4.5, 2.8 Hz, 1 H, 3-H), 2.97 (m, 1 H, 2-H), 2.93 (d, *J* = 16.4 Hz, 1 H, 5-H), 2.81 (dd, *J* = 18.9, 2.8 Hz, 1 H, 1-H), 2.64 (d, *J* = 16.4 Hz, 1 H, 5-H), 2.57 (dd, *J* = 18.9, 3.0 Hz, 1 H, 1-H), 2.46 (dd, *J* = 7.5, 1.5 Hz, 1 H, 4-H), 2.29 (s, 3 H, $COCH_3$), 1.44 (s, 9 H, *t*Bu), 1.01 (d, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 204.3, 202.4, 169.9, 167.4, 88.1, 82.0, 56.604, 39.5, 38.7, 36.8, 35.9, 28.7, 28.2, 16.7 ppm. IR (KBr): $\tilde{\nu}$ = 2998, 2982, 2920, 1773, 1746, 1720, 1705, 1696, 1437, 1368, 1301, 1178, 1105, 1022, 983 cm^{-1}. HRMS (ESI) calcd. for $C_{16}H_{22}O_6Na$ [M + Na]$^+$ 333.1314; found 333.1319.

Synthesis of *tert*-Butyl 2-(5-Hydroxy-2-oxo-2*H*-pyran-6-yl)acetate (4): *c*Hex_2NMe (2 μL, 0.01 mmol) was added to a stirred solution of **1** (20 mg, 0.09 mmol) in *t*BuOH (1 mL). After the system had been stirred at room temperature for 20 h, the reaction was quenched by addition of a saturated aqueous NH_4Cl solution. The aqueous phase was extracted by diethyl ether (×3) and the combined extracts were washed with brine, dried with Na_2SO_4, and filtered. Concentration of the solution gave a yellow oil (19 mg, 95%) as the product, which was used directly in the next steps without further purification: R_f = 0.41 (silica gel, hexanes/ethyl acetate 1:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.75 (br, 1 H, OH), 7.29 (d, *J* = 9.8 Hz, 1 H, *CH*=CH), 6.22 (d, *J* = 9.8 Hz, 1 H, *CH*=CH), 3.64 (s, 2 H, $CH_2COOtBu$), 1.51 (s, 9 H, *t*Bu) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.2, 161.5, 142.2, 139.9, 138.0, 115.6, 84.8, 38.5, 28.1 ppm. IR (KBr): $\tilde{\nu}$ = 3425, 3111, 2981, 2932, 2847, 1735, 1370, 1251, 1152, 1080, 1007, 847 cm^{-1}. HRMS (ESI) calcd. for $C_{11}H_{14}O_5Na$ [M + Na]$^+$ 249.0739; found 249.0736.

Synthesis of Methyl 2-[5-(*tert*-Butyldimethylsilyloxy)-2-oxo-2*H*-pyran-6-yl]acetate (2): Imidazole (0.52 g, 7.68 mmol) was added to a stirred solution of **17** (0.35 g, 1.92 mmol) in DMF (15 mL), followed by TBSCl (0.72 g, 4.8 mmol). The reaction mixture was stirred at room temperature and monitored by TLC until all the starting material had been consumed. The mixture was then poured onto ice and the aqueous layer was extracted with diethyl ether (×3). The combined extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. Silica gel flash column chromatography of the residue gave a yellow oil (0.51 g, 89%) as the product: R_f = 0.51 (silica gel, hexanes/ethyl acetate 3:1). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.13 (d, *J* = 9.9 Hz, 1 H, *CH*=CH), 6.20 (d, *J* = 9.9 Hz, 1 H, *CH*=CH), 3.73 (s, 3 H, OCH_3), 3.56 (s, 2 H, CH_2COOCH_3), 0.97 (s, 9 H, *t*Bu), 0.18 [s, 6 H, Si*t*Bu(CH_3)$_2$] ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 168.5, 161.0, 145.9, 142.0, 136.1, 115.4, 52.5, 34.6, 25.6, 18.1, –4.2 ppm. IR (KBr): $\tilde{\nu}$ = 2954, 2930, 2886, 2859, 1742, 1646, 1553, 1435, 1349, 1258, 1214, 1122, 990, 842, 783 cm^{-1}. HRMS (ESI) calcd. for $C_{14}H_{22}O_5NaSi$ [M + Na]$^+$ 321.1134; found 321.1133.

General Procedure for the Lewis-Acid-Promoted Diels–Alder Cycloaddition between Methyl 2-[5-(*tert*-Butyldimethylsilyloxy)-2-oxo-2*H*-pyran-6-yl]acetate (2) and Methyl Acrylate. Synthesis of Methyl 1-(2-Methoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]octane-8-*endo*-carboxylate (19a) and Methyl 1-(2-Methoxy-2-oxoethyl)-3,6-dioxo-2-oxabicyclo[2.2.2]octane-8-*exo*-carboxylate (19b): The appropriate Lewis acid (0.3 mmol) was added to a stirred solution of **2** (0.1 mmol) and methyl acrylate (0.5 mmol) in CH_2Cl_2 (1.5 mL).

After the reaction mixture had been stirred at room temperature for 3 d, TLC indicated remaining starting material. Either further Lewis acid (0.2 mmol) was added until TLC indicated the consumption of the starting material or the reaction was stopped after 10 d. The reaction mixture was then worked up by addition of a saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted with diethyl ether (×3). The combined extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash chromatography to give the DA products **19a** and **19b** (16 mg, 60%, *endo*/*exo* = 7.7:1 with $BF_3{\cdot}OEt_2$ as the Lewis acid). The **19a**/**19b** ratio was determined by comparison of ^1H NMR signals (δ_{endo} = 3.24 ppm, δ_{exo} = 3.03 ppm). Compound **19a** (white solid): m.p. 149–151 °C; R_f = 0.45 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.78 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.41 (dt, J = 5.9, 2.9 Hz, 1 H, 2-H), 3.24 (m, 1 H, 3-H), 2.94 (d, J = 16.6 Hz, 1 H, 5-H), 2.82 (d, J = 16.6 Hz, 1 H, 5-H), 2.71 (m, 3 H, 1-H, 4-H), 2.62 (dd, J = 15.5, 4.8 Hz, 1 H, 4-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 201.28, 171.31, 170.87, 167.40, 84.69, 81.87, 53.02, 39.47, 37.62, 37.56, 35.06, 30.96, 28.15 ppm. IR (KBr): $\tilde{\nu}$ = 3005, 2983, 2959, 2918, 1770, 1748, 1736, 1443, 1375, 1268, 1200, 1099, 1035, 1008, 964, 750 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{14}O_7Na$ $[M + Na]^+$ 293.0637; found 293.0638. Compound **19b** (white solid): m.p. >200 °C (dec.), R_f = 0.30 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.78 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3), 3.38 (d, J = 2.1 Hz, 1 H, 2-H), 3.03 (ddd, J = 10.7, 6.9, 1.5 Hz, 1 H, 3-H), 2.89 (dd, J = 24.8, 16.5 Hz, 2 H, 5-H), 2.81 (dd, J = 19.1, 3.0 Hz, 1 H, 1-H), 2.75 (dd, J = 15.3, 6.8 Hz, 1 H, 4-H), 2.64 (dd, J = 19.1, 2.7 Hz, 1 H, 1-H), 2.54 (dd, J = 15.3, 10.9 Hz, 1 H, 4-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 202.0, 171.7, 169.7, 168.8, 83.8, 53.1, 52.2, 40.5, 40.1, 38.3, 36.5, 31.4 ppm. IR (KBr): $\tilde{\nu}$ = 3056, 2988, 2955, 2842, 1773, 1735, 1438, 1369, 1266, 1214, 1177, 1038, 1008, 735 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{14}O_7Na$ $[M + Na]^+$ 293.0637; found 293.0635.

General Procedure for the Lewis-Acid-Promoted Diels–Alder Cycloaddition between Methyl 2-[5-(*tert*-Butyldimethylsilyloxy)-2-oxo-2*H*-pyran-6-yl]acetate (2) and Methyl Vinyl Ketone. Synthesis of Methyl 2-(8-*endo*-Acetyl-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl)-acetate (20a) and Methyl 2-(8-*exo*-Acetyl-3,6-dioxo-2-oxabicyclo[2.2.2]octan-1-yl)acetate (20b): The appropriate Lewis acid (0.12 mmol) was added to a stirred solution of **2** (0.1 mmol) and freshly distilled methyl vinyl ketone (0.5 mmol) in CH_2Cl_2 (1.5 mL). The resulting mixture was stirred at room temperature and monitored by TLC until the consumption of the starting material. The reaction was worked up by careful addition of a saturated aqueous $NaHCO_3$ solution and the aqueous layer was extracted with diethyl ether (×3). The combined extracts were washed with brine, dried with Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel flash chromatography to give the DA products **20a** and **20b** (23 mg, 90%, *endo*/*exo* = 12:1 with $BF_3{\cdot}OEt_2$ as the Lewis acid). The **20a**/**20b** ratio was determined by comparison of ^1H NMR signals: δ_{endo} = 3.30 ppm, δ_{exo} = 3.09 ppm). Compound **20a** (white solid): m.p. 134–135 °C; R_f = 0.36 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.71 (s, 3 H, OCH_3), 3.37 (dd, J = 5.6, 2.8 Hz, 1 H, 2-H), 3.30 (m, 1 H, 3-H), 2.94 (d, J = 16.6 Hz, 1 H, 5-H), 2.81 (d, J = 16.6 Hz, 1 H, 5-H), 2.63 (m, 4 H, 1-H, 4-H), 2.27 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 204.1, 200.7, 170.8, 168.8, 84.8, 52.2, 44.7, 39.0, 36.2, 34.3, 29.4, 28.7 ppm. IR (KBr): $\tilde{\nu}$ = 3029, 2975, 2955, 2940, 2847, 1773, 1751, 1715, 1434, 1382, 1256, 1194, 1113, 1040, 1003, 966 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{14}O_6Na$ $[M + Na]^+$ 277.0688; found 277.0691. Compound **20b** (yellow oil): R_f = 0.19 (silica gel, hexanes/ethyl acetate 1:1). ^1H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 3.72 (s, 3 H, OCH_3), 3.35 (dt, J = 4.8, 2.8 Hz, 1 H, 2-H), 3.09 (ddd, J = 10.7, 6.9, 1.8 Hz, 1 H, 3-H), 2.88 (m, 3 H, 5-H, 1-H), 2.72 (dd, J = 15.1, 6.9 Hz, 1 H, 4-H), 2.66 (dd, J = 19.1, 2.8 Hz, 1 H, 1-H), 2.45 (dd, J = 15.1, 10.7 Hz, 1 H, 4-H), 2.30 (s, 3 H, $COCH_3$) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 204.21, 202.08, 169.57, 168.83, 83.77, 52.23, 47.86, 39.50, 38.33, 36.50, 30.00, 28.32 ppm. IR (KBr): $\tilde{\nu}$ = 3056, 2959, 2917, 2843, 1771, 1733, 1713, 1436, 1363, 1266, 1169, 1031, 732 cm^{-1}. HRMS (ESI) calcd. for $C_{12}H_{14}O_6Na$ $[M + Na]^+$ 277.0688; found 277.0685.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures, ^1H NMR and ^{13}C NMR spectra for all the new compounds, ORTEP diagrams of compounds **14b**–**16b**.

Acknowledgments

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[16] The X-ray crystallographic structures of **14**–**16b** are available in the Supporting Information

[17] Detailed procedures are available in the Supporting Information.

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