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The Dihydropyrone Diels–Alder Reaction: Development and Application to the Synthesis of Highly Functionalized 1-Oxa-4-decalones

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Abstract—A facile method for the synthesis of highly functionalized 1-oxadecalone derivatives is described via the Diels–Alder reaction of 2,3-dihydro-4-pyrone dienophiles with electron rich dienes. By this process a variety of functional groups and substitution patterns can be incorporated into the oxadecalone framework.

Introduction

The 1-oxadecalin ring system serves as the core of a variety of structurally diverse and biologically interesting natural products.[1] As part of an effort geared toward the synthesis of one such compound, the PAF antagonist phomactin A (**1**, Fig. 1),[2] we recently reported a facile approach to the synthesis of 1-oxadecalones **2**.[3] Our goal in this endeavor was to develop an expedient method for the synthesis of the basic 6,6-ring system, while at the same time providing sufficient functionality to allow for subsequent synthetic manipulation. Toward this end, we anticipated that the Diels–Alder reaction of a suitably functionalized 2,3-dihydro-4-pyrone dienophile **3** with a diene **4** would effectively meet these criteria.

In practice, we found that dihydropyrone dieneophiles of this type undergo cycloaddition reactions with electron rich dienes under both thermal[3a] and Lewis acid catalyzed[3b] conditions. This work demonstrated for the first time that dihydropyrones could be used effectively as dienophiles in the Diels–Alder reaction, and validated this strategy as an efficient entry to the basic 1-oxadecalin framework. As such, we anticipated that further development of this method would provide useful insights for the use of this protocol in the synthesis of more complex molecules that contain the 1-oxadecalin ring system.[4] Herein we describe such studies, and report our findings with regard to the scope of the dihydropyrone Diels–Alder reaction in its application to the synthesis of highly functionalized 1-oxadecalone derivatives.

Results and Discussion

Though the Diels–Alder reaction has been much utilized for the synthesis of six membered rings, extension of this methodology to the use of dienophiles that contain a β-oxygen substituent has remained fairly limited. Indeed, though several related examples had appeared in the literature,[5] to the best of our knowledge 2,3-dihydro-4-pyrones had not previously been employed in this application. As such, our first objective was to demonstrate the feasibility of this method for the synthesis of 1-oxadecalones **2**.

Toward this end, we initially chose to explore the reactivity of 2,3-dihydro-4-pyrones of type **3** that contained an electron withdrawing substituent at C5 (Fig. 2).[6] Though a

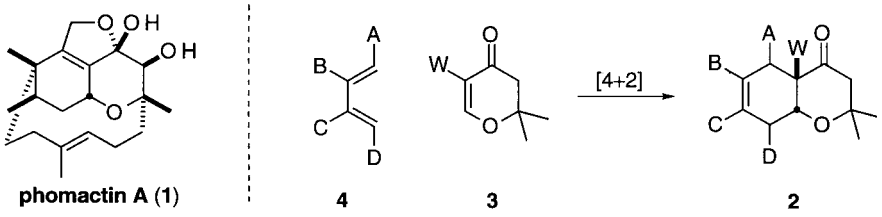

Figure 1.

Keywords: Diels–Alder reactions; cycloaddition; pyrone.

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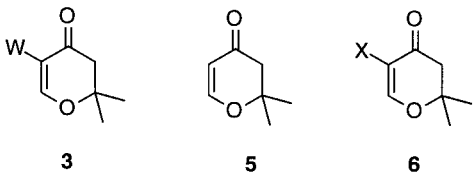


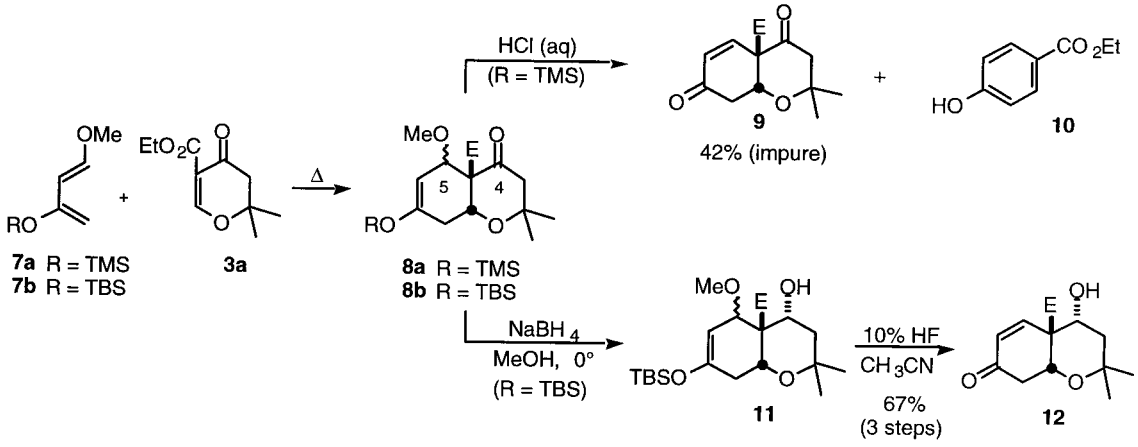
Figure 2.

variety of other 2,3-dihydro-4-pyrone derivatives are readily available,[7] we anticipated that the presence of such a functionality at C5 would enhance the reactivity of these substrates as dienophiles relative to that of the parent dihydropyrone (**5**). In addition, we anticipated that the use of an electron rich diene would facilitate the cycloaddition reaction with these rather unconventional dienophiles.

The 5-carbethoxy dihydropyrone derivative **3a** was thus prepared and evaluated in the Diels–Alder reaction with Danishefsky's diene **7a** (Scheme 1). As anticipated, the reactivity of the dihydropyrone **3a** was such that high temperatures were required to initiate the cycloaddition. Thus, treatment of the dihydropyrone **3a** with 5 equiv. of diene **7a** at 190°C under sealed tube conditions provided the Diels–Alder adduct **8a**, which was directly hydrolyzed to give the 1-oxadecalone **9** in ca. 42% yield (impure). Inspection of the crude reaction mixture revealed the presence of varying amounts of ethyl *p*-hydroxybenzoate (**10**) that could not be separated from the desired product. Since formation of this aromatic ester was believed to commence by hydration of the C4 ketone (e.g. **9**),[8] we anticipated that reduction of this moiety prior to hydrolysis of the silyl enol ether would circumvent this degradative pathway. Unfortunately, direct synthetic manipulation of the silyl enol ether **8a** (R=TMS) was limited by the poor hydrolytic stability of this intermediate. However, use of the *tert*-butyldimethylsilyl derivative of Danishefsky's diene (**7b**)[9] allowed for the isolation of a stable cycloadduct **8b** (5α:5β=4:1) that could be partially purified by chromatography. Use of the more thermally stable diene **7b** had the added benefit of minimizing diene decomposition over the course of the reaction. As such, not only were we able to reduce the amount of diene present in the reaction mixture, but the transformation could now be effected at lower temperature, and without the use of a sealed tube.

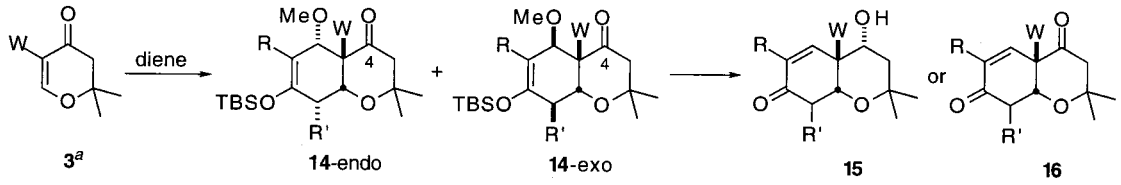
With the cycloadduct **8b** in hand, reduction of the C4 ketone ($NaBH_4$) and hydrolysis of the enol ether provided the corresponding 1-oxadecalone **12** in 67% overall yield without accompanying aromatization.[10] Alternatively the cycloadduct **8b** could be reduced with $LiAlH_4$ to give, upon hydrolysis, the corresponding diol **13** in 59% overall yield as a single diastereomer (Table 1, entry 1).

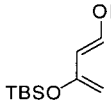
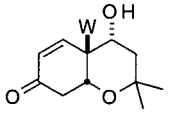
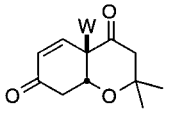
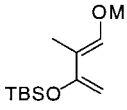
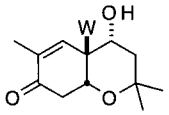
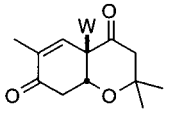
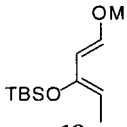
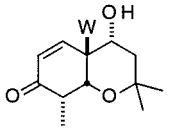
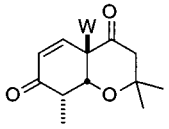
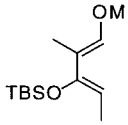
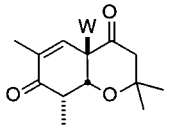
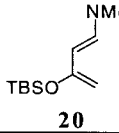
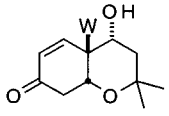
As shown in Table 1, a variety of activated dihydropyrones **3** undergo cycloaddition reactions with electron rich dienes.[11] In addition to the C5 ester (**3a**), nitrile (**3b**), sulfone (**3c**), and ketone (**3d**) functionalities are also suitable activating groups for these dihydropyrones (entries 2–4). In each of these cases, initial cycloaddition favors formation of the *endo* product (e.g. **14**-*endo*),[12] with varying levels of diastereoselectivity. As shown (entries 2, 6 and 10), highest levels of selectivity are observed with the C5 nitrile (**3b**), which reacts with 1-methoxy-3-silyloxy dienes to give a 10–16:1 ratio of isomers with the *endo* adduct predominating. Similar levels of selectivity (10:1) are observed with the C5 sulfone (entries 3, 7, and 11). In these cases, secondary orbital interactions of the diene with the C5 nitrile and sulfone substituents are presumably less significant than those with the ring ketone at C4.[13] To a lesser extent, such differences are also apparent in the Diels–Alder reactions of the 5-carbethoxy derivative **3a**, the diastereoselectivity of which is generally 4:1 in reactions with 1-methoxy-3-silyloxy dienes (entries 1, 5, 9, and 12). In the case of the C5 ketone (**5d**), in which secondary orbital interactions between the diene and substituents at C4 and C5 are expected to be similar, little diastereoselectivity is observed (entries 4 and 8). It is interesting to note that the use of the related 1-dimethylamino-2-silyloxy diene **20** (Rawal's diene)[14] results in a significant increase in diastereoselectivity (20:1) in the Diels–Alder reaction with dihydropyrone **3a**. Though in many of these examples the stereochemistry of the cycloadduct is of little consequence, in the current application, use of the more highly substituted dienes **18** and **19** (entries 9–12) result in the formation of stereocenter at C8 that is not destroyed upon hydrolysis of the intermediate enol ether. In cases where a significant amount of the *exo* adduct is present, separation of the diastereomers can be achieved by silica gel chromatography.



Scheme 1.

Table 1. Synthesis of 1-oxadecalone derivatives using activated dienes



entry	diene	conditions	endo:exo[b]	product	yield[c]
1	 **7b**	**3a**, 110°C, 24 h; $LiAlH_4$; HF	4 : 1	 **13** W = CH_2OH	59%
2		**3b**, 110°C, 24 h; $NaBH_4$; HF	16 : 1	**12b** W = CN	73%[d]
3	**7b**	**3c**, 110°C, 24 h; pTsOH	10 : 1	 **12c** W = SO_2Ph	88%
4		**3d**, 110°C, 24 h; HF	1.2 : 1	**12d** W = $COCH_3$	72%
5	 **17**	**3a**, 110°C, 24 h; $NaBH_4$; pTsOH	3.4 : 1	 **21a** W = CO_2Et	56%[d]
6		**3b**, 110°C, 36 h; $NaBH_4$; pTsOH	16 : 1	**21b** W = CN	68%[d]
7	**17**	**3c**, 110°C, 24 h; pTsOH	10 : 1	 **21c** W = SO_2Ph	78%
8		**3d**, 110°C, 40 h; HF	1.1 : 1	**21d** W = $COCH_3$	69%
9	 **18**	**3a**, 110°C, 24 h; $NaBH_4$; HF	4 : 1	 **22a** W = CO_2Et	61%[d]
10		**3b**, 110°C, 24 h; $NaBH_4$; HF	10 : 1	**22b** W = CN	70%[d]
11	**18**	**3c**, 110°C, 42 h; pTsOH	10 : 1	 **22c** W = SO_2Ph	64%
12	 **19**	**3a**, 110°C, 48 h; HF	4 : 1	 **23a** W = CO_2Et	52%
13	 **20**	**3a**, 25°C, 45 min; $LiAlH_4$; HF	20 : 1	 **13** W = CH_2OH	65%

[a] **3a** W=CO_2Et; **3b** W=CN; **3c** W=SO_2Ph; **3d** W=$COCH_3$.
[b] Ratios were obtained by analysis of ^1H NMR spectra of the crude reaction mixtures. Relative stereochemistry was determined by NOE studies on the individual cycloadducts.
[c] Isolated yield.
[d] In addition to the compound shown, ca. 10% of the β C4 alcohol was also isolated.

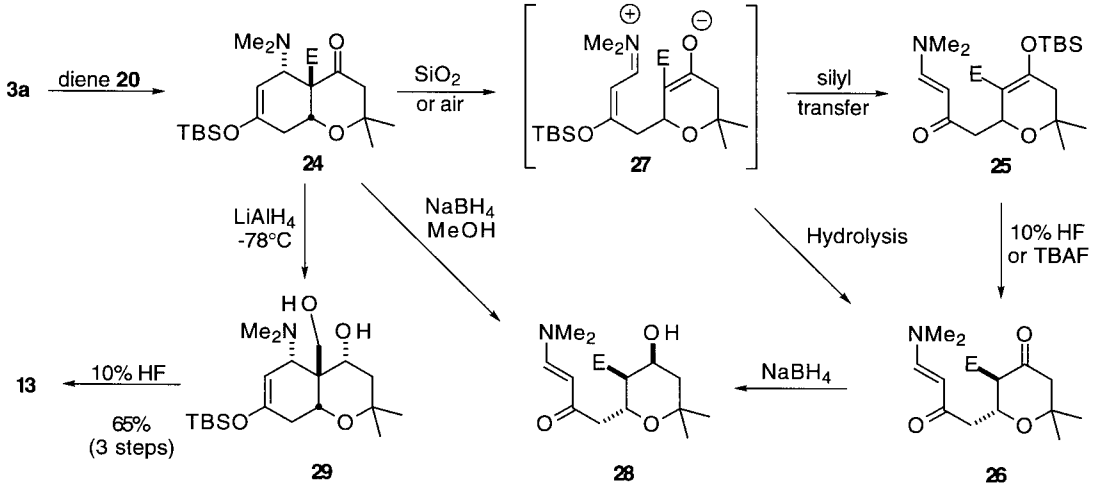
As was observed in the reaction of dihydropyrone **3a** with Danishefsky's diene (cf. Scheme 1), direct hydrolysis of the initially formed cycloadducts is often complicated by competing aromatization of the carbocyclic ring. However, notable differences in the stability of product oxadecalones of type **16** were observed depending on the nature of the electron withdrawing substituent at C4a. For example, 1-oxadecalones **16** that contained ester (W=CO_2Et) and nitrile (W=CN) functionalities at the ring junction are generally subject to rapid aromatization, necessitating reduction at C4, while those with a C4a sulfone (W=SO_2Ph) can be readily purified by silica gel chromatography (entries 3, 7, and 11). In these latter cases, the bulky phenylsulfone substituent at C4a may impede hydration of the C4 carbonyl, and thus shuts down the degradative pathway.[8] In certain cases, even those derivatives that are

prone to aromatization can be isolated with the C4 ketone intact. For example, the oxadecalone **12d** that bears a keto substitutent at the ring junction, as well as at C4, can be isolated in 72% overall yield (entry 4). Though this derivative is subject to the degradative aromatization process, purification can be achieved by recrystallization from hexanes:CH_2Cl_2. In this case, attempts to selectively reduce the C4 carbonyl with $NaBH_4$ result in the formation of a complex mixture of diastereomers. Though the need to reduce the C4 ketone prior to hydrolysis in the majority of these cases adds length to the synthetic sequence, overall yields for these 2–3 step processes are generally excellent.

Though the cycloaddition reactions of the type described in Table 1 generally require elevated temperatures, reaction of the more strongly activated Rawal's diene **20** occurs quite readily at room temperature in the absence of a solvent. However, although clean conversion of reactants **3a** and **20** to the corresponding cycloadduct **24** (E=CO_2Et) is observed by ^{1}H NMR analysis of the crude reaction mixture, only ring cleavage products **25** (45%) and **26** (46%) are obtained on attempted purification (Scheme 2). Formation of these compounds is thought to arise by fragmentation of the initially formed cycloadduct to give a zwitterionic intermediate **27** that can then undergo silyl transfer or hydrolysis to give products **25** and **26** respectively. Presumably, the presence of the bulky, electron rich dimethylamino group at C5 facilitates this ring cleavage due to the proximity of the β electron withdrawing substituents (e.g. ester and ketone).[15] As such, we anticipated that this problem could be circumvented by reduction of the C4 ketone in analogy to efforts described above. Unfortunately, reduction of the cycloadduct **24** with $NaBH_4$ was accompanied by ring cleavage providing the tetrahydropyran **28** as a single diastereomer. In this case, ring cleavage presumably occurs prior to reduction.[16] Indeed, reduction of the tetrahydropyrone **26** under like conditions also provides alcohol **28**. As the rate of ring cleavage is enhanced in the presence of a polar medium, we anticipated that the use of a less polar solvent might facilitate reduction prior to cleavage of the C4a/C5 bond. In practice, treatment of the crude cycloadduct **24** with $LiAlH_4$ in Et_2O at −78°C provided the desired enone **13** in 65% overall yield from dihydropyrone **3a**. Though the difficulties encountered with use of the 1-dimethylaminodiene **20** for the synthesis of 1-oxadecalone derivatives of type **15** make use of this system less practical for routine use, the enhanced reactivity of such systems may allow for the preparation of 1-oxadecalone derivatives that are less stable to high reaction temperatures or are derived from less highly activated dihydropyrone dienophiles.

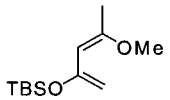
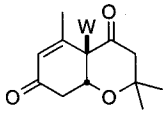
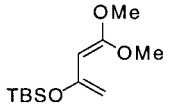
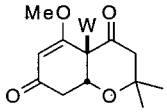
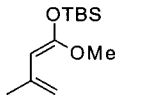
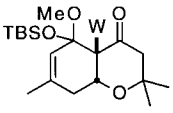
In order to further assess the scope of the dihydropyrone Diels–Alder reaction, a variety of additional dienes were screened in this application. In particular, dienes were chosen which allowed us to evaluate both steric and electronic factors in the success of this reaction. Toward this end, we first examined a series of electron rich dienes **30**–**32** that contained additional substitution at C1 (Table 2). Here, Diels–Alder reaction of the 1-methoxy-1-methyl-3-silyloxydiene **30** with dihydropyrones **3a** and **3b** proceeded under standard conditions (110°C, 24 h) to give, upon hydrolysis, the corresponding 1-oxadecalone derivatives **33** (entries 1 and 2). Though the overall yields in the synthetic sequence suffer somewhat from the increased steric requirements of this diene **30**, useful amounts of the 1-oxadecalone products **33** can still be obtained by this procedure. In any event, the steric restraints imposed by the presence of a *cis* substituent at C1 are overcome in the trioxygenated diene **31**, reaction of which with dihydropyrones **3** occurs in excellent yields at room temperature (entries 3–6). In these cases, the product oxadecalones (**33** and **34**) bear a non-hydrogen substituent at C5 and are no longer subject to degradative aromatization of the carbocyclic ring. Thus reduction of the C4 ketone is not required prior to hydrolysis.

Despite the success of dihydropyrone Diels–Alder reactions that employ dienes **30** and **31**, the related system **32** does not participate in cycloaddition reactions with dihydropyrone dienophiles. Indeed, this system is not reactive enough to undergo cycloaddition at ambient conditions, while at higher temperature, decomposition of the diene predominates.[17] Though under Lewis acid catalyzed conditions reaction of the diene **32** with dihydropyrones **3a** and **3b** is quite facile, in these cases the unsaturated ester **36** (Fig. 3) is the



Scheme 2.

Table 2. Synthesis of 1-oxadecalone derivatives using trisubstituted dienes

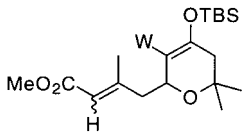
entry	diene	conditions[a]	product		yield[b]
1		**3a**, 110°C, 60 h; HF		**33a** W = CO_2Et	48%
2		**3b**, 110°C, 40 h; HF		**33b** W = CN	40%
	30				
3		**3a**, 25°C, 8 h; pTsOH		**34a** W = CO_2Et	85%
4		**3b**, 25°C, 20 h; pTsOH		**34b** W = CN	75%
5		**3c**, 25°C, 20 h; H_2, Pd/C[c]		**34c** W = SO_2Ph	60%
6	**31**	**3d**, 25°C, 36 h; HF		**34d** W = $COCH_3$	56%
7		**3a**, 25°C, 48 h		**35a** W = CO_2Et	0%
8		**3b**, 25°C, 48 h		**35b** W = CN	0%
	32				

[a] **3a** W=CO_2Et; **3b** W=CN; **3c** W=SO_2Ph; **3d** W=$COCH_3$.
[b] Isolated yield.
[c] Under these conditions, competing reduction of the product enone is not observed.

only product isolated from the reaction mixture. None of the corresponding cycloadducts **35** are observed, even when the reaction is quenched at low temperatures.

We next examined the ability of dihydropyrones **3** to act as dienophiles in the Diels–Alder reactions with dienes that contained a single oxygen functionality (Table 3). In this context we first explored the reaction of commercially available 1-methoxybutadiene (**37**) with the dihydropyrone ester **3a**. In refluxing toluene, no cycloaddition products were observed even after extended reaction times. However, the desired Diels–Alder adduct **40a** can be obtained in 54% yield when the reaction is carried out at 260°C in toluene for 72 h (entry 1). Examination of the crude reaction mixture by ^1H NMR indicated that the cycloadducts were formed as a 10:1 mixture of diastereomers with the *endo* isomer predominating. The nitrile **3b** and sulfone **3c** (entries 2 and 3) also undergo the desired cycloaddition reaction. Here, the reactions proceed at lower temperatures (200°C), and with higher levels of stereoselectivity. Indeed, in neither case was any of the *exo* diastereomer apparent in the ^1H NMR of the crude reaction mixture.[5d] These results are consistent with the higher levels of selectivity observed for nitrile **3b** and sulfone **3c** derivatives versus that of the ester **3a** with more highly activated dienes (cf. Table 1).

Two additional monooxygenated dienes **38** and **39** were also examined in this application, albeit with limited success (entries 4–7). In general, we found that monooxygenated dienes of these types do not undergo thermal Diels–Alder reactions with dihydropyrones **3**, perhaps due to the instability of the dienes at temperatures required for the cycloaddition reaction. An exception was noted in the case of the nitrile derivative **3b** which reacts with the hindered diene **39** to provide oxadecalone **42b** in moderate yield (38%) after hydrolysis of the intermediate cycloadduct.[18] In any event, we have since demonstrated that the low reactivity of these monooxygenated dienes **38** and **39** with dihydropyrone **3a** can be overcome by the use of Lewis acid.[3b] Indeed, Diels–Alder reactions of diene **38** and **39** with dihydropyrone **3a** in the presence of $ZnCl_2$ (THF, 25°C, 2 h) provides the corresponding 1-oxadecalones **42a** and **42b** in 73% and 76% overall yields, respectively, upon hydrolysis of the intermediate enol ethers.[3b] Under these same conditions 1-methoxybutadiene (**39**) shows no reaction with either of these dihydropyrones.[19]



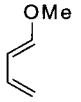
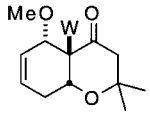
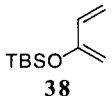
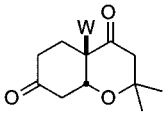
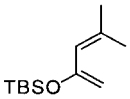
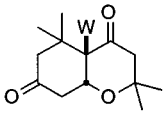
36a W = CO_2Et (80%)
36b W = CN (83%)

Figure 3.

In light of our results with the monooxygenated dienes, it is perhaps not surprising to note that to date we have been unable to identify conditions under which unactivated dienes **43**–**45** (Fig. 4) will participate in the Diels–Alder reaction with dihydropyrone dienophiles **3**. Indeed, in these cases, none of the corresponding cycloadducts are observed, even after 72 h at temperatures up to 300°C (sealed tube). The use of Lewis acid catalysts has been equally unsuccessful in this specific application. At the same time, we have begun to explore the reactivity of the related dihydropyrones **5** and **6** (Fig. 2, X=Br, I) as dienophiles in the Diels–Alder reaction. As anticipated, compounds of these types are significantly less reactive than the dihydropyrones of type **3**, and do not undergo cycloaddition, even with highly activated dienes such as Rawal's diene **20** and the trioxygenated diene **31**. Preliminary results also suggest that compounds of these types are unreactive toward electron poor dienes such as **46** and **47**.

In conclusion, the Diels–Alder reaction of 2,3-dihydro-4-pyrone dienophiles provides a facile entry to the synthesis of highly functionalized 1-oxadecalin derivatives. Under thermal conditions, dihydropyrone dienophiles **3**, that contain an electron withdrawing substituent at C5, undergo cycloaddition reactions with electron rich dienes under relatively mild conditions. Though more vigorous conditions are

Table 3. Synthesis of 1-oxadecalone derivatives using monooxygenated dienes

entry	diene	conditions [a]	endo:exo [b]	product	yield [c]
1	 **37**	**3a**, 260°C (sealed tube), 72 h	10 : 1	 **40a** W = CO_2Et	54%
2		**3b**, 200°C (sealed tube), 72 h	>99 : 1	**40b** W = CN	68%
3		**3c**, 200°C (sealed tube), 72 h	>99 : 1	**40c** W = SO_2Ph	65%
4	 **38**	**3a**, 110°C, 24 h	---	 **41a** W = CO_2Et	0%
5	 **39**	**3a**, 110°C, 24 h; HF	---	 **42a** W = CO_2Et	0%
6		**3b**, 110°C, 60 h; HF	---	**42b** W = CN	38%
7		**3c**, 200°C, 72 h; HF	---	**42c** W = SO_2Ph	0%

[a] **3a** W=CO_2Et; **3b** W=CN; **3c** W=SO_2Ph; **3d** W=$COCH_3$.
[b] Ratios were obtained by analysis of ^1H NMR spectra of the crude reaction mixtures. Relative stereochemistry was determined by NOE studies on the individual cycloadducts.
[c] Isolated yield.

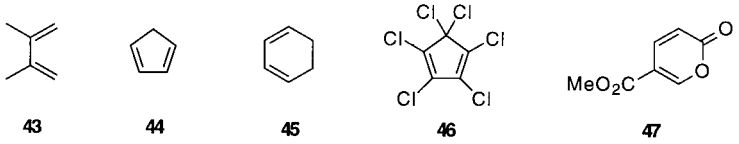


Figure 4.

required for the use of less strongly activated dienes, in general, the desired oxadecalone products are obtained in high overall yields. By this process, a variety of functional groups and substitution patterns can be incorporated into the basic oxadecalin framework. This feature should provide for significant flexibility in the synthesis of more complex substrates. Overall, the dihydropyrone Diels–Alder reaction is a synthetically useful process that allows for the preparation of highly functionalized 1-oxadecalone derivatives in a straightforward manner. Studies aimed at the application of this methodology toward the synthesis of complex molecules are currently ongoing. These results will be reported in due course.

Experimental

General methods

All air sensitive reactions were performed in oven dried glassware under an atmosphere of argon. Reaction solvents were dried over CaH_2 (benzene, dichloromethane) or sodium/benzophenone ketyl (toluene, tetrahydrofuran) and were distilled just prior to use. All other reagents were reagent grade and purified where necessary. Melting points are uncorrected. ^1H NMR spectra were recorded on a Bruker WM 360 spectrometer. Chemical shifts are reported in ppm, downfield from tetramethylsilane using residual $CHCl_3$ (δ 7.27) as the internal standard. ^{13}C NMR spectra were recorded on a Bruker WM-360 (90 MHz) spectrometer in $CDCl_3$ with complete proton decoupling. Residual $CHCl_3$ (δ 77.0 ppm) was used as the internal standard. IR spectra were obtained with a Mattson Cygnus 25 instrument. High resolution mass spectra were obtained by the University of Iowa Mass Spectrometry Laboratory. Elemental Analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

General procedure for the reduction of cycloadducts with $NaBH_4$

A solution of the Diels–Alder adduct (1 mmol) in MeOH was cooled to 0°C and $NaBH_4$ (1.5 mmol) was added. After 1 h, the reaction mixture was quenched with saturated, aqueous NH_4Cl, warmed to room temperature, and extracted with CH_2Cl_2. The combined organics were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to provide the crude alcohol.

General procedures for the acid catalyzed hydrolysis of enol ethers

Method A. To a solution of the enol ether (1 mmol) in wet THF (3 mL) was added a catalytic amount of pTsOH (25 mg). The resulting mixture was stirred at room temperature for 2 h, after which time aqueous, saturated $NaHCO_3$ was added, and the reaction mixture diluted with CH_2Cl_2. The layers were separated, and the aqueous extracted with additional CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and the solvent removed in vacuo.

Method B. To a solution of the enol ether (1 mmol) in 4 mL

CH_3CN was added 0.60 mL 10% HF in CH_3CN. The resulting mixture was stirred for 2 h at room temperature, then saturated, aqueous $NaHCO_3$ was added, and the reaction mixture diluted with CH_2Cl_2. The layers were separated, and the aqueous extracted with additional CH_2Cl_2. The combined organics were dried over $MgSO_4$, filtered, and the solvent removed in vacuo.

1-Oxadecalone 12a. A solution of diene **7b** (0.068 g, 0.32 mmol) and dihydropyrone **3a** (0.021 g, 0.106 mmol) in 0.5 mL toluene was warmed to reflux, and stirred for 24 h. The reaction mixture was then cooled to room temperature, concentrated in vacuo, and the residue passed through a short silica gel column (hexanes:EtOAc, 7:1, containing 1% Et_3N) to remove lower R_f materials. The partially purified Diels–Alder adduct was reduced with $NaBH_4$ according to the general procedure, then hydrolyzed directly (Method B). The residue was purified by flash chromatography (SiO_2; hexanes: EtOAc, 2:1) to provide the enone (0.019 g, 67%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 6.90 (1H, dd, J=10.3, 2.3 Hz), 6.23 (1H, d, J=10.3 Hz), 4.51 (1H, dd, J=12.5, 4.6 Hz), 4.36 (1H, dd, J=5.6, 2.9 Hz), 4.24 (2H, q, J=7.2 Hz), 2.63 (1H, dd, J=17.1, 2.7 Hz), 2.60 (1H, br s, OH), 2.52 (1H, dd, J=17.1, 3.1 Hz), 1.71 (1H, dd, J=13.1, 4.6 Hz), 1.44 (1H, t, J=12.8 Hz), 1.28 (3H, t, J=7.2 Hz), 1.26 (3H, s), 1.16 (3H, s). ^{13}C NMR ($CDCl_3$): δ 196.9, 171.8, 141.5, 131.5, 73.0, 70.3, 69.0, 62.2, 54.1, 41.9, 40.1, 31.1, 22.5, 14.1. IR (film): 3437, 1725, 1686 cm^{-1} HRMS (EI): Calcd for $C_{14}H_{20}O_5$ ($[M]^+$): 268.1311, found: 268.1291.

1-Oxadecalone 12b. A solution of diene **7b** (0.058 g, 0.27 mmol) and dihydropyrone **3b** (0.015 g, 0.10 mmol) in 0.5 mL toluene was warmed to reflux. After 24 h, the reaction mixture was cooled to room temperature, concentrated in vacuo, and the crude Diels–Alder adduct reduced with $NaBH_4$, then hydrolyzed (Method B). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 7:3) to give 0.016 g (73%) of the enone as a white solid (mp 124–125°C). ^{1}H NMR ($CDCl_3$): δ 6.78 (1H, dd, J=10.2, 2.6 Hz), 6.28 (1H, d, J=10.2 Hz), 4.35 (2H, m), 2.91 (1H, dd, J=17.0, 2.7 Hz), 2.79 (1H, br d, J=4.5 Hz), 2.67 (1H, ddd, J=17.0, 3.2, 0.9 Hz), 1.74 (1H, dd, J=13.4, 4.5 Hz), 1.38 (1H, m), 1.23 (3H, s), 1.15 (3H, s). ^{13}C NMR ($CDCl_3$): δ 195.1, 136.6, 133.1, 118.5, 73.7, 70.0, 68.6, 43.0, 41.7, 39.6, 30.8, 22.3. IR (film): 3442, 2238, 1692 cm^{-1} HRMS (EI): Calcd for $C_{12}H_{15}O_3N$ ($[M]^+$): 221.1052, found: 221.1065.

1-Oxadecalone 12c. A solution of diene **7b** (0.084 g, 0.39 mmol) and dihydropyrone **3c** (0.035 g, 0.13 mmol) in 0.5 mL toluene was warmed to reflux. After 24 h, the reaction mixture was cooled to room temperature, the solvent removed in vacuo, and the crude Diels–Alder adduct hydrolyzed (Method A). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 7:3) to afford the enone as a white solid (0.038 g, 88%). ^{1}H NMR ($CDCl_3$): δ 7.72 (3H, m), 7.58 (2H, m), 6.31 (1H, dd, J=10.3, 2.4 Hz), 6.22 (1H, dd, J=10.3, 0.7 Hz), 5.43 (1H, dt, J=4.4, 2.2 Hz), 3.38 (1H, dd, J=17.3, 4.4 Hz), 3.36 (1H, d, J=13.9 Hz), 2.69 (1H, ddd, J=17.3, 2.2, 0.7 Hz), 2.46 (1H, d, J=13.9 Hz), 1.42 (3H, s), 1.07 (3H, s). ^{13}C NMR ($CDCl_3$): δ 199.6, 194.0, 136.2, 135.1, 134.7, 133.0, 130.5, 129.1, 75.8, 74.8, 68.5, 49.3, 41.3, 29.4, 27.2. IR (film): 1727, 1692 cm^{-1} HRMS (FAB): Calcd for $C_{17}H_{18}O_5S$ ($[M+H]^+$): 335.09532, found: 335.0944.

1-Oxadecalone 12d. A solution of diene **7b** (0.260 g, 1.21 mmol) and dihydropyrone **3d** (0.100 g, 0.606 mmol) in 4 mL toluene was warmed to reflux and stirred for 24 h. The reaction mixture was cooled to room temperature, concentrated in vacuo, and the residue passed through a short silica gel column (hexanes:EtOAc, 7:1, containing 1% Et_3N) to remove lower R_f materials. The resulting Diels–Alder adduct was concentrated in vacuo, then hydrolyzed directly (Method B). The product was recrystallized from hexanes/CH_2Cl_2 to give the enone **12d** as a white solid (0.101 g, 72%). ^{1}H NMR ($CDCl_3$): δ 6.88 (1H, dd, J=10.2, 2.7 Hz), 6.25 (1H, d, J=10.2 Hz), 5.10 (1H, m), 2.68 (1H, dd, J=17.1, 3.1 Hz), 2.58 (2H, m), 2.50 (1H, d, J=13.7 Hz), 2.30 (3H, s), 1.32 (3H, s), 1.21 (3H, s). ^{13}C NMR ($CDCl_3$): δ 204.2, 201.3, 194.4, 140.8, 130.9, 75.3, 70.9, 69.1, 49.6, 40.9, 29.8, 29.4, 25.3. IR (film): 1722, 1707, 1696 cm^{-1} HRMS (EI): Calcd for $C_{13}H_{16}O_4$ ($[M]^+$): 236.1048, found: 236.1041.

1-Oxadecalone 13. Diene **20** (0.24 g, 1.1 mmol) and dihydropyrone **3a** (0.53 g, 0.26 mmol) were combined in the absence of solvent and stirred at room temperature for 45 min. The crude cycloadduct was dissolved in ether (2 mL) and the resulting solution cooled to −78°C. $LiAlH_4$ (0.055 g, 1.5 mmol) was added, and the reaction mixture allowed to warm gradually to room temperature over 3 h. After 16 h, it was diluted with wet ether (7 mL), treated sequentially with 3 M NaOH (0.08 mL) and H_2O (0.24 mL), then stirred for 10 min. The resulting suspension was filtered through celite and concentrated in vacuo. The crude material (**29**) was then hydrolyzed (Method B). The residue was purified by flash chromatography (SiO_2; $CHCl_3$:MeOH, 50:1–20:1) to provide the enone (0.039 g, 65%) as a white solid (mp 126–127°C). ^{1}H NMR: δ 7.01 (1H, dd, J=10.4, 2.5 Hz), 6.22 (1H, d, J=10.4 Hz), 4.33 (1H, m), 4.12 (1H, dd, J=5.7, 3.0 Hz), 3.97 (1H, dd, J=10.6, 5.5 Hz), 3.79 (1H, dd, J=10.6, 3.4 Hz), 2.90 (1H, d, J=3.0 Hz), 2.77 (1H, dd, J=17.5, 3.2 Hz), 2.58 (1H, m), 2.50 (1H, ddd, J=17.5, 3.0, 1.0 Hz), 1.72 (1H, dd, J=12.7, 4.6 Hz), 1.49 (1H, t, J=12.7 Hz), 1.24 (3H, s), 1.17 (3H, s). ^{13}C NMR: δ 197.7, 146.5, 131.5, 72.7, 69.5, 68.2, 66.9, 46.6, 41.9, 40.9, 31.3, 22.6. IR (film): 3414, 1670 cm^{-1}. Anal. Calcd for $C_{12}H_{18}O_5$: C, 63.70%; H, 8.02%. Found: C, 63.36%; H, 8.05%.

1-Oxadecalone 21a. A solution of diene **17** (0.082 g, 0.41 mmol) and dihydropyrone **3a** (0.041 g, 0.21 mmol) in 0.5 mL toluene was warmed to reflux. After 24 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The crude Diels–Alder adduct was reduced with $NaBH_4$, then subjected to hydrolysis (Method A). The residue was purified by flash chromatography (SiO_2; hexanes: EtOAc, 3:1) to give the enone (0.033 g, 57%) as a pale yellow liquid. ^{1}H NMR ($CDCl_3$): δ 6.61 (1H, t, J=1.2 Hz), 4.42 (1H, dt, J=12.3, 3.8 Hz), 4.30 (1H, dd, J=5.2, 2.3 Hz), 4.20 (2H, q, J=7.1 Hz), 2.63 (1H, dd, J=17.0, 2.2 Hz), 2.51 (1H, dd, J=17.0, 2.7 Hz), 2.50 (1H, d, J=3.4 Hz; OH), 1.86 (3H, d, J=1.2 Hz), 1.67 (1H, dd, J=12.7, 4.6 Hz), 1.42 (1H, t, J=12.7 Hz), 1.25 (3H, t,

J=7.1 Hz), 1.22 (3H, s), 1.12 (3H, s). ^{13}C NMR ($CDCl_3$): δ 197.1, 172.4, 137.7, 135.9, 72.8, 70.3, 69.2, 62.0, 54.1, 41.9, 40.0, 31.1, 22.5, 16.1, 14.1. IR (film): 3457, 1724, 1683 cm^{-1} HRMS (EI): Calcd for $C_{15}H_{22}O_5$ ($[M]^+$): 282.1467, found: 282.1482.

1-Oxadecalone 21b. A solution of diene **17** (0.082 g, 0.44 mmol) and dihydropyrone **3b** (0.083 g, 0.42 mmol) in 0.5 mL toluene was warmed to reflux. After 36 h, the reaction mixture was cooled to room temperature and concentrated in vacuo. The crude Diels–Alder adduct was reduced with $NaBH_4$, then subjected to hydrolysis (Method A). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 3:1) to give 0.027 g (68%) of the enone as a pale yellow solid (mp 151–152°C). ^{1}H NMR ($CDCl_3$): δ 6.51 (1H, br s), 4.32 (2H, m), 2.91 (1H, dd, J=17.0, 2.7 Hz), 2.70 (2H, m), 1.87 (3H, d, J=1.1 Hz), 1.72 (1H, dd, J=13.3, 4.5 Hz), 1.41 (1H, t, J=12.8 Hz), 1.23 (3H, s), 1.14 (3H, s). ^{13}C NMR ($CDCl_3$): δ 195.2, 140.0, 130.8, 119.1, 73.6, 70.1, 69.0, 43.5, 41.8, 39.5, 30.9, 22.3, 16.0. IR (film): 3455, 2237, 1686 cm^{-1} HRMS (EI): Calcd for $C_{13}H_{17}O_3N$ ($[M]^+$): 235.1208, found: 235.1222.

1-Oxadecalone 21c. A solution of diene **17** (0.052 g, 0.26 mmol) and dihydropyrone **3c** (0.034 g, 0.13 mmol) in 0.5 mL toluene was warmed to reflux. After 24 h, the reaction mixture was cooled to room temperature, the solvent removed in vacuo, and the crude Diels–Alder adduct hydrolyzed (Method A). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 3:1) to afford the enone as a white solid (0.035 g, 78%; mp 144–145°C).^{1}H NMR ($CDCl_3$): δ 7.71 (3H, m), 7.57 (2H, m), 6.07 (1H, m), 5.39 (1H, m), 3.37 (1H, dd, J=17.4, 4.3 Hz), 3.31 (1H, d, J=14.0 Hz), 2.69 (1H, dd, J=17.4, 2.2 Hz), 2.44 (1H, d, J=14.0 Hz), 1.83 (3H, d, J=1.5 Hz), 1.40 (3H, s), 1.06 (3H, s). ^{13}C NMR ($CDCl_3$): δ 200.1, 194.3, 140.2, 135.0, 131.0, 130.4, 129.0, 75.7, 75.2, 68.6, 49.4, 41.4, 29.5, 27.1, 16.4. IR (film): 1724, 1686 cm^{-1}. HRMS (EI): Calcd for $C_{18}H_{20}O_5S$ ($[M]^+$): 348.1031, found: 348.1045.

1-Oxadecalone 21d. A solution of diene **17** (0.073 g, 0.37 mmol) and dihydropyrone **3d** (0.031 g, 0.18 mmol) in 0.5 mL toluene was warmed to reflux. After 40 h, the reaction mixture was cooled to room temperature, the solvent removed in vacuo, and the crude Diels–Alder adduct hydrolyzed (Method B). The product was recrystallized from hexanes:ethyl acetate (10:1) to give the desired enone as a white solid (0.032 g, 69%; mp 85–86°C). ^{1}H NMR ($CDCl_3$): δ 6.59 (1H, m), 5.04 (1H, m), 2.67 (1H, dd, J=17.2, 3.0 Hz), 2.56 (1H, dd, J=17.2, 3.2 Hz), 2.51 (2H, s), 2.28 (3H, s), 1.90 (3H, d, J=1.5 Hz), 1.29 (3H, s), 1.20 (3H, s). ^{13}C NMR ($CDCl_3$): δ 204.9, 202.4, 194.9, 137.8, 135.6, 75.4, 71.2, 69.3, 49.7, 41.0, 30.0, 29.5, 25.3, 16.2. IR (film): 1705, 1686 cm^{-1}. HRMS (FAB): Calcd for $C_{14}H_{18}O_4$ ($[M+Na]^+$): 273.1103, found: 273.1090.

1-Oxadecalone 22a. A solution of diene **18** (0.29 g, 1.27 mmol) and dihydropyrone **3a** (0.13 g, 0.63 mmol) in 2.5 mL toluene was refluxed for 24 h. The reaction mixture was cooled to room temperature, concentrated in vacuo and passed through a short silica gel column (15:1, hexanes:EtOAc, containing 1% Et_3N). The partially purified Diels–Alder adduct was reduced with $NaBH_4$, then hydrolyzed (Method B). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 2:1) to provide the *endo* (0.082 g, 46%) and *exo* diastereomers (0.027 g, 15%) as white solids (*endo* mp 108–109°C). *endo*: ^{1}H NMR ($CDCl_3$): δ 6.81 (1H, dd, J=10.3, 2.9), 6.20 (1H, d, J=10.3 Hz), 4.45 (1H, dt, J=12.5, 4.4 Hz), 4.25 (2H, q, J=7.2 Hz), 4.17 (1H, t, J=2.6 Hz), 2.55 (1H, dq, J=6.9, 1.9 Hz), 2.30 (1H, d, J=4.2 Hz), 1.70 (1H, dd, J=13.1, 4.7 Hz), 1.42 (1H, t, J=13.0 Hz), 1.28 (3H, t, J=7.0 Hz), 1.23 (3H, s), 1.15 (3H, d, J=6.9 Hz), 1.13 (3H, s). ^{13}C NMR ($CDCl_3$): δ 199.5, 172.3, 140.3, 131.4, 75.4, 72.7, 69.6, 62.1, 55.3, 44.2, 40.5, 31, 22.6, 14.1, 11.3. IR (film): 3417, 1684 cm^{-1}. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.63; H, 7.74. *exo*: ^{1}H NMR ($CDCl_3$): δ 6.90 (1H, dd, J=10.6, 2.6 Hz), 6.11 (1H, d, J=10.5 Hz), 4.46 (1H, dd, J=12.7, 4.5 Hz), 4.28 (1H, t, J=2.4 Hz), 4.21 (2H, m), 2.56 (1H, dq, J=8.0, 2.7 Hz), 2.38 (1H, s, br), 1.66 (1H, dd, J=12.8, 4.6 Hz), 1.41 (1H, t, J=12.6 Hz), 1.28 (3H, t, J=7.0 Hz), 1.26 (3H, s), 1.14 (3H, s), 1.03 (3H, d, J=8.1 Hz). ^{13}C NMR ($CDCl_3$): δ 201.0, 173.2, 141.6, 129.4, 75.1, 72.9, 71.0, 61.9, 52.5, 47.1, 40.6, 31.2, 22.6, 13.9, 13.7.

1-Oxadecalone 22b. A solution of diene **18** (0.1 g, 0.5 mmol) and dihydropyrone **3b** (0.015 g, 0.1 mmol) in toluene (0.5 mL) was refluxed for 24 h. The reaction mixture was cooled to room temperature, concentrated in vacuo and passed through a short silica gel column (hexanes:EtOAc, 15:1, containing 1% Et_3N). The partially purified Diels–Alder adduct was then reduced with $NaBH_4$, and hydrolyzed (Method B). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 2:1) to provide enone **22b** (0.032 g, 70%) as a white solid (mp 95–96°C). ^{1}H NMR ($CDCl_3$): δ 6.73 (1H, dd, J=10.3, 2.5 Hz), 6.29 (1H, d, J=10.0 Hz), 4.36 (1H, m), 4.15 (1H, t, J=2.1 Hz), 3.0 (1H, m), 2.96 (1H, dq, J=1.9, 6.9 Hz), 1.76 (1H, dd, J=13.5, 4.7 Hz), 1.40 (1H, d, J=12.9 Hz), 1.23 (3H, s), 1.22 (3H, d, J=6.5 Hz), 1.15 (3H, s). ^{13}C NMR ($CDCl_3$): δ 197.7, 135.2, 133.3, 118.7, 74.8, 73.4, 69.0, 44.5 (2C), 39.9, 30.8, 22.3, 11.0. IR (film): 3370, 2239, 1694 cm^{-1}. Anal. Calcd for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.15; H, 7.18; N, 5.74.

1-Oxadecalone 22c. A solution of diene **18** (0.06 g, 0.28 mmol) and dihydropyrone **3c** (0.015 g, 0.056 mmol) in toluene (0.5 mL) was refluxed for 42 h. The reaction mixture was cooled to room temperature, concentrated in vacuo and passed through a short silica gel column (hexanes:EtOAc, 15:1, containing 1% Et_3N). The partially purified Diels–Alder adduct was then hydrolyzed directly (Method A). The residue was purified by recrystallization from hexanes to provide enone **22c** (0.013 g, 64%) as a white solid (mp 132–133°C). ^{1}H NMR ($CDCl_3$): δ 7.74 (3H, m), 7.62 (2H, m), 6.25 (2H, m), 5.30 (1H, dd, J=3.5, 2.2 Hz), 3.51 (1H, m), 3.40 (1H, d, J=14.0 Hz), 2.48 (1H, d, J=13.8 Hz), 1.42 (3H, s), 1.27 (3H, d, J=6.8 Hz), 1.08 (3H, s). ^{13}C NMR ($CDCl_3$): δ 199.8, 196.8, 135.1, 135.0, 134.8, 133.0, 130.4, 129.1, 75.7, 75.6, 73.2, 49.2, 43.0, 29.3, 26.6, 10.6. IR (film): 1727, 1694 cm^{-1}. HRMS (EI): Calcd for $C_{18}H_{20}O_5S$ (M^+): 348.1032, found: 348.1031.

1-Oxadecalone 23a. A solution of diene **19** (2.2 g,

8.9 mmol) and dihydropyrone **3a** (0.59 g, 3.0 mmol) in toluene (10 mL) was refluxed for 48 h. The reaction mixture was cooled to room temperature, concentrated in vacuo and passed through a short silica gel column (hexanes:EtOAc, 20:1, containing 2% Et_3N). The individual Diels–Alder adducts were then hydrolyzed (Method B), and the residues purified by flash chromatography (SiO_2; hexanes:EtOAc, 5:1) to provide *endo* (0.37 g, 42%) and *exo* (0.092 g, 10%) adducts as yellow oils. *endo*: ^{1}H NMR ($CDCl_3$): δ 6.30 (1H, m), 4.76 (1H, t, J=2.6 Hz), 4.30 (2H, m), 2.57 (1H, dq, J=2.6, 6.9 Hz), 2.50 (2H, d, J=2.4 Hz), 1.89 (3H, m), 1.31 (3H, t, J=7.1 Hz), 1.28 (3H, s), 1.24 (3H, s), 1.23 (3H, d, J=6.8 Hz). ^{13}C NMR ($CDCl_3$): δ 203.5, 197.8, 168.1, 137.2, 133.95, 76.6, 75.2, 63.7, 62.2, 49.7, 43.5, 30.1, 24.5, 16.2, 14.1, 11.2. IR (film): 1742, 1709, 1684. HRMS (FAB): Calcd for $C_{16}H_{24}O_5Na$ ($[M+Na]^+$): 317.1367, found: 317.1344. *exo*: ^{1}H NMR ($CDCl_3$): δ 6.33 (1H, m), 4.82 (1H, t, J=2.2, 2.9 Hz), 4.29 (2H, m), 2.75 (1H, dq, J=7.7, 2.6 Hz), 2.50 (2H, s), 1.90 (3H, m), 1.32 (3H, s), 1.31 (3H, t, J=7.1 Hz), 1.25 (3H, s), 1.06 (3H, d, J=7.8 Hz). ^{13}C NMR ($CDCl_3$): δ 203.5, 199.5, 168.8, 135.2, 134.5, 76.1, 75.0, 62.2, 61.8, 49.4, 46.3, 30.1, 24.6, 16.4, 14.4, 14.0. IR (film): 1748, 1726, 1683. HRMS (FAB): Calcd for $C_{16}H_{24}O_5Na$ ($[M+Na]^+$): 317.1367, found: 317.1344.

1-Oxadecalone 33a. A solution of diene **30** (0.082 g, 0.44 mmol) and dihydropyrone **3a** (0.034 g, 0.17 mmol) in 0.5 mL toluene was warmed to reflux. After 60 h, the reaction mixture was cooled to room temperature, the solvent removed in vacuo, and the crude Diels–Alder adduct hydrolyzed (Method B). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 4:1) to give (0.023 g, 48%) the enone as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.14 (1H, br s), 4.92 (1H, t, J=3.0 Hz), 4.29 (2H, m), 2.68 (1H, dd, J=17.1, 2.9 Hz), 2.46 (1H, dd, J=17.1, 3.0 Hz), 2.37 (2H, s), 1.97 (3H, d, J=1.4 Hz), 1.29 (9H, m). ^{13}C NMR ($CDCl_3$): δ 203.3, 194.8, 167.5, 150.0, 129.6, 75.8, 72.6, 66.2, 62.2, 50.9, 40.6, 30.5, 23.4, 22.0, 14.0. IR (film): 1737, 1717, 1687 cm^{-1} HRMS (EI): Calcd for $C_{15}H_{20}O_5$ ($[M]^+$): 280.1312, found: 280.1311.

1-Oxadecalone 33b. A solution of diene **30** (0.077 g, 0.39 mmol) and dihydropyrone **3b** (0.020 g, 0.13 mmol) in 0.5 mL toluene was warmed to reflux. After 40 h, the reaction mixture was cooled to room temperature, the solvent removed in vacuo, and the crude Diels–Alder adduct was hydrolyzed directly (Method B). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 4:1) to give 0.012 g (40%) of the enone as a pale yellow solid (mp 153–154°C). ^{1}H NMR ($CDCl_3$): δ 6.18 (1H, d, J=1.5 Hz), 4.63 (1H, t, J=3.0 Hz), 2.86 (1H, dd, J=16.8, 2.9 Hz), 2.78 (1H, dd, J=16.8, 3.1 Hz), 2.42 (2H, m), 1.90 (3H, d, J=1.5 Hz), 1.31 (3H, s), 1.24 (3H, s). ^{13}C NMR ($CDCl_3$): δ 197.5, 193.0, 144.6, 130.6, 114.2, 76.8, 72.4, 56.0, 49.7, 40.6, 30.3, 22.9, 20.3. IR (film): 2243, 1726, 1689 cm^{-1} HRMS (EI): Calcd for $C_{13}H_{15}O_3N$ ($[M+H]^+$): 256.0950, found: 256.0939.

1-Oxadecalone 34a. A mixture of diene **31** (0.714 g, 2.92 mmol) and dihydropyrone **3a** (0.193 g, 0.980 mmol) was stirred in the absence of solvent at room temperature for 8 h, then the crude Diels–Alder adduct hydrolyzed (Method A). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 2:1) to afford the enone as a white solid (0.220 g, 85%), mp 100–101°C. ^{1}H NMR ($CDCl_3$): δ 5.57 (1H, s), 4.84 (1H, t, J=3.0 Hz), 4.28 (2H, dq, J=7.1, 1.3 Hz), 3.77 (3H, s), 2.65 (1H, dd, J=17.4, 2.7 Hz), 2.46 (1H, dd, J=17.4, 3.0 Hz), 2.43 (1H, d, J=13.6 Hz), 2.33 (1H, d, J=13.6 Hz), 1.31 (3H, s), 1.23 (3H, t, J=7.1 Hz), 1.21 (3H, s). ^{13}C NMR ($CDCl_3$): δ 200.2, 194.8, 168.2, 166.5, 103.6, 76.0, 72.0, 66.3, 62.3, 56.5, 50.6, 40.2, 30.4, 23.2, 13.9. IR (film): 1742, 1722, 1667 cm^{-1} HRMS (FAB): Calcd for $C_{15}H_{21}O_6$ ($[M+H]^+$): 297.1338, found: 297.1338.

1-Oxadecalone 34b. A mixture of diene **31** (0.043 g, 0.198 mmol) and dihydropyrone **3b** (0.023 g, 0.152 mmol) was dissolved in 0.5 mL benzene and stirred at room temperature for 24 h. The solvent was removed in vacuo, and the crude Diels–Alder adduct subjected to hydrolysis (Method A). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 3:1) to afford the enone as a white solid (0.028 g, 75%). ^{1}H NMR ($CDCl_3$): δ 5.61 (1H, s), 4.57 (1H, dd, J=2.9 Hz), 3.78 (3H, s), 2.84 (1H, dd, J=17.1, 3.0 Hz), 2.74 (1H, dd, J=17.1, 2.8 Hz), 2.42 (2H, m), 1.32 (3H, s), 1.23 (3H, s). ^{13}C NMR ($CDCl_3$): δ 194.6, 193.2, 163.6, 113.7, 104.2, 77.1, 72.3, 57.3, 55.6, 49.6, 40.3, 30.3, 22.8. IR (film): 2219, 1735, 1686 cm^{-1} HRMS (FAB): Calcd for $C_{13}H_{15}O_4N$ ($[M+Na]^+$): 272.0899, found: 272.0893.

1-Oxadecalone 34c. A mixture of diene **31** (0.415 g, 1.70 mmol) and dihydropyrone **3c** (0.094 mg, 0.35 mmol) was dissolved in 1.5 mL benzene and stirred at room temperature for 24 h. The solvent was removed in vacuo, and the crude Diels–Alder adduct redissolved in 2 mL ethyl acetate. A catalytic amount of 10% Pd/C (0.018 g) was added, and the resulting mixture carefully degassed, then stirred under an atmosphere of H_2 for 16 h. After that time, the reaction mixture was filtered through celite and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 3:2) to afford the enone as a white solid (0.070 g, 60%). ^{1}H NMR ($CDCl_3$): δ 8.00 (2H, m), 7.61 (1H, m), 7.51 (2H, m), 5.71 (1H, s), 5.10 (1H, dd, J=4.1, 1.9 Hz), 3.54 (1H, dd, J=17.9, 4.1 Hz), 3.45 (3H, s), 2.62 (1H, dd, J=17.9, 1.9 Hz), 2.37 (1H, d, J=13.2 Hz), 2.29 (1H, d, J=13.2 Hz), 1.25 (3H, s), 1.24 (3H, s). ^{13}C NMR ($CDCl_3$): δ 197.3, 195.1, 163.0, 139.1, 134.2, 131.0, 128.1, 106.7, 79.3, 75.9, 70.1, 56.1, 52.6, 41.0, 30.2, 22.9. IR (film): 1732, 1667 cm^{-1} HRMS (FAB): Calcd for $C_{18}H_{21}O_6S$ ($[M+H]^+$): 365.1059, found: 365.1056.

1-Oxadecalone 34d. A mixture of diene **31** (0.157 g, 0.642 mmol) and dihydropyrone **3d** (0.054 mg, 0.32 mmol) was dissolved in 0.5 mL benzene and stirred at room temperature for 36 h. The solvent was removed in vacuo, and the crude Diels–Alder adduct subjected to hydrolysis according to the general procedure (Method B). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 2:1) to afford the enone as a white solid (0.033 g, 56%). ^{1}H NMR ($CDCl_3$): δ 5.60 (1H, s), 4.84 (1H, t, J=3.0 Hz), 3.81 (3H, s), 2.58 (1H, dd, J=17.7, 2.5 Hz), 2.46 (1H, d, J=13.0 Hz), 2.45 (1H, dd, J=17.7, 3.2 Hz), 2.40 (1H, d, J=13.0 Hz), 2.25 (3H, s), 1.28 (3H, s), 1.21 (3H, s). ^{13}C NMR ($CDCl_3$): δ 203.0, 201.8, 195.2, 168.4, 104.4, 76.2, 71.8,

70.2, 56.5, 51.6, 40.2, 30.6, 29.3, 23.3. IR (film): 1732, 1712, 1661 cm^{-1} HRMS (FAB): Calcd for $C_{14}H_{18}O_5$ ($[M+H]^+$): 267.1232, found: 267.1207.

1-Oxadecalone 40a. A solution of diene **37** (0.17 mL, 1.7 mmol) and dihydropyrone **3a** (0.056 g, 0.28 mmol) in toluene (2 mL) was heated in a sealed tube for 72 h at 260°C. The reaction mixture was cooled to room temperature, concentrated, and the residue purified by flash chromatography (SiO_2; hexanes:EtOAc, 4:1) to provide **40a** (0.042 g, 54%) as a yellow oil. ^1H NMR ($CDCl_3$): δ 6.07 (1H, m), 5.83 (1H, m), 4.68 (1H, d, J=4.9 Hz), 4.37 (1H, d, J=4.0 Hz), 4.20 (2H, q, J=7.2 Hz), 3.33 (3H, s), 2.70 (1H, d, J=16.1 Hz), 2.46 (1H, d, J=16.1 Hz), 2.40 (1H, m), 2.23 (1H, m), 1.35 (3H, s), 1.33 (3H, s), 1.25 (3H, t, J=7.2 Hz). ^{13}C NMR ($CDCl_3$): δ 205.3, 169.1, 125.6, 123.8, 73.6, 73.5, 66.3, 62.5, 61.7, 58.3, 51.2, 30.7, 28.4, 26.4, 14.0. IR (film): 1735, 1712 cm^{-1}. HRMS (FAB): Calcd for $C_{15}H_{22}O_5Na$ ($[M+Na]^+$): 305.1368, found: 305.1374.

1-Oxadecalone 40b. A solution of diene **37** (0.08 mL, 0.83 mmol) and dihydropyrone **3b** (0.021 g, 0.14 mmol) in toluene (1 mL) was heated in a sealed tube for 72 h at 200°C. The reaction mixture was cooled to room temperature, concentrated, and the residue purified by flash chromatography (SiO_2; hexanes:EtOAc, 4:1) to provide **40b** (0.022 g, 68%) as a colorless oil. ^1H NMR ($CDCl_3$): δ 6.02 (2H, m), 4.36 (1H, d, J=4.7 Hz), 4.02 (1H, m), 3.36 (3H, s), 2.80 (1H, d, J=16.0 Hz), 2.64 (1H, m), 2.50 (1H, d, J=16.0 Hz), 2.49 (1H, m), 1.34 (3H, s), 1.31 (3H, s). ^{13}C NMR ($CDCl_3$): δ 199.5, 127.2, 121.8, 117.0, 74.4, 66.2, 58.4, 52.4, 51.6, 30.7, 28.2, 25.3. IR (film): 2244, 1717 cm^{-1}. Anal. Calcd for $C_{13}H_{17}O_3N$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.25; H, 7.27; N, 5.77.

1-Oxadecalone 40c. A solution of diene **37** (0.07 mL, 0.66 mmol) and dihydropyrone **3c** (0.03 g, 0.11 mmol) in toluene (1 mL) was heated in a sealed tube for 72 h at 200°C. The reaction mixture was cooled to room temperature, concentrated, and the residue purified by flash chromatography (SiO_2; hexanes:EtOAc, 4:1) to provide **14c** (0.025 g, 65%) as a white solid (mp 135–136°C). ^1H NMR ($CDCl_3$): δ 7.86 (2H, m), 7.70 (1H, m), 7.57 (2H, m), 6.00 (2H, m), 5.00 (1H, d, J=6.2 Hz), 4.03 (1H, m), 3.14 (3H, s), 3.00 (1H, m), 2.73 (1H, d, J=15.4 Hz), 2.46 (1H, m), 2.45 (1H, d, J=15.4 Hz), 1.27 (3H, s), 1.20 (3H, s). ^{13}C NMR ($CDCl_3$): δ 201.3, 136.6, 134.4, 130.9, 128.9, 128.7, 121.1, 76.3, 73.8, 72.8, 64.7, 58.6, 51.3, 30.5, 29.6, 27.0. IR (film): 1723 cm^{-1}. Anal. Calcd for $C_{18}H_{22}O_5S$: C, 61.69; H, 6.33. Found: C, 61.83; H, 6.37.

1-Oxadecalone 42b. A solution of diene **39** (0.12 g, 0.66 mmol) and dihydropyrone **3b** (0.020 g, 0.13 mmol) in 0.5 mL toluene was warmed to reflux. After 72 h, the reaction mixture was cooled to room temperature, the solvent removed in vacuo, and the crude Diels–Alder adduct hydrolyzed (Method B). The residue was purified by flash chromatography (SiO_2; hexanes:EtOAc, 4:1) to give 0.011 g (38%) of the enone as a white solid (mp 130–132°C). ^1H NMR ($CDCl_3$): δ 4.71 (1H, dd, J=5.8, 1.8 Hz), 2.95 (1H, ddd, J=15.6, 5.8, 0.7 Hz), 2.79 (1H, d, J=13.9 Hz), 2.65 (1H, dt, J=15.6, 2.2 Hz), 2.60 (1H, d, J=16.6 Hz), 2.49 (1H, d, J=16.6 Hz), 2.23 (1H, dd, J=13.9, 2.2 Hz), 1.32 (3H, s), 1.29 (3H, s), 1.24 (3H, s), 1.22 (3H, s). ^{13}C NMR ($CDCl_3$): δ 204.5, 199.0, 117.3, 74.6, 73.6, 58.1, 53.6, 51.1, 43.6, 41.6, 30.5, 28.8, 26.4, 25.0. IR (film): 2244, 1722, 1712 cm^{-1} HRMS (EI): Calcd for $C_{14}H_{19}O_3N$ ($[M]^+$): 249.1365, found: 249.1340.

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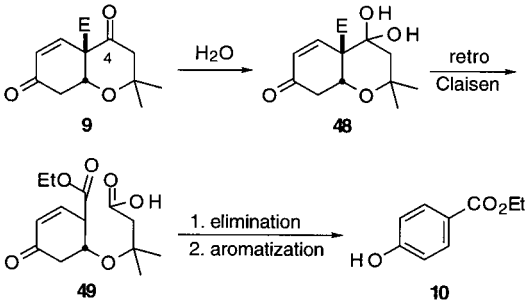
8. Presumably this contaminant is derived from the corresponding 1-oxadecalone **9** via hydration of the C4 ketone (**48**) with subsequent retro-Claisen reaction (**49**) and aromatization as indicated below. Pure ethyl *p*-hydroxybenzoate (**10**) could be isolated by chromatography. However, due to continued decomposition on silica gel, this ester could not be completely separated from oxadecalone **9**.



9. Routinely, dienes such as **7b** are prepared by deprotonation of the corresponding ketone with KHMDS followed by treatment

with TBDMSCl. (See also, Ref. [14]). Dienes obtained by this procedure are generally >90% pure and are used without further purification.

10. In addition to this product, ca. 12% of the corresponding β C4 hydroxy derivative was isolated.

11. For reviews on preparation and use of activated dienes in Diels–Alder reactions see: (a) Barluenga, J.; Suarez-Sobrino, A.; Lopez, L. A. *Aldrichimica Acta* **1999**, *32*, 4. (b) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753.

12. For our purposes, the *endo* isomer is defined as that in which approach of the diene is directed by the 4-keto substituent of the dihydropyrone ring. Thus, the methoxy substituent at C5 and the W substituent at C4a will be *trans* in the *endo*-cycloadduct. See: Seth, P. P.; Totah, N. I. *Org. Lett.* **1999**, *1*, 1401.

13. Sauer, J.; Sustmann, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19* 779.

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15. Formation of the cycloadduct **24** via a concerted process is supported by the observation that the ^{1}H NMR of the crude reaction mixture after 45 min shows only the cycloadduct **24**. With increasing reaction times, the cleavage product **26** begins to appear such that, under anhydrous conditions, compound **26** can be isolated cleanly in 86% yield after 8 h at room temperature. Attempts to convert the ring opened products **25** and **26** to the corresponding 1-oxadecalin (**8**) under either acidic or basic conditions were unsuccessful.

16. The *trans* relationship between substituents at C4 and C6 in the tetrahydropyrone **28** suggests that reduction of the C4 carbonyl occurs after cleavage of the C4a/C5 bond of cycloadduct **24**. Reduction of the *cis* fused oxadecalin system (**24**) would be expected to occur from the convex face to provide the α hydroxyl function (cf. **29**).

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18. Yields of oxadecalone **42b** do not improve when the cycloaddition is carried out under sealed tube conditions (200°C). In addition to observed decomposition, there is some indication that the cycloaddition of the C5 nitrile **3b** may be reversible at these temperatures.

19. In general, we have observed that monoxygenated dienes that contain the activating substituent at C1 are significantly less reactive under Lewis acid catalyzed conditions than are those in which the substituent is at C2 (Ref. 3b).