Dihydropyrones as Dienophiles in the Diels−Alder Reaction: Application to the Synthesis of 1-Oxadecalones

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The 1-oxadecalin unit serves as the structural core for a number of naturally occurring compounds, including the reduced furochroman phomactin A (**1**, Figure 1),[1] as well as a variety of diterpenoids such as forskolin (**2**),[2] jamesoniellide E (**3**),[3] and scutorientalin D (**4**).[4] Many of these compounds exhibit intriguing biological properties, though the diverse array of structural features present in these systems make them challenging synthetic targets.

Our interest in the development of new strategies for the synthesis of complex substrates, in particular toward the preparation of the PAF antagonist phomactin A, led us to consider a general approach to the synthesis of highly functionalized 1-oxadecalone derivatives.[5] Our goal in this endeavor was to develop an expedient entry to the basic 6,6-ring system, while at the same time providing sufficient functionality to allow for subsequent synthetic manipulation. Toward this end, we envisaged that the Diels−Alder reaction of a suitably functionalized 2,3-dihydro-4-pyrone with a diene would effectively meet these criteria. Though several related examples have appeared using chromone[6] and pyrone[7] derivatives as dienophiles in [4 + 2] cycloaddition reactions, to the best of our knowledge, dihydropyrones of this type have not previously been utilized in this application. Herein we report the successful implementation of this strategy for the synthesis of highly functionalized 1-oxadecalone derivatives.

In practice, we chose to explore the reactivity of 2,3-dihydro-4-pyrones that contain an electron-withdrawing substituent at C5 (e.g., **5**).[8] We anticipated the need for this functionality to enhance the reactivity of these substrates as dienophiles relative to that of the parent dihydropyrones.[9] As the C5 substituent of the dihydropyrone would ultimately be located at the ring junction of the 1-oxadecalone unit, incorporation of diverse functionality at this position would provide added flexibility in the application of this method to the synthesis of more complex systems. As shown,

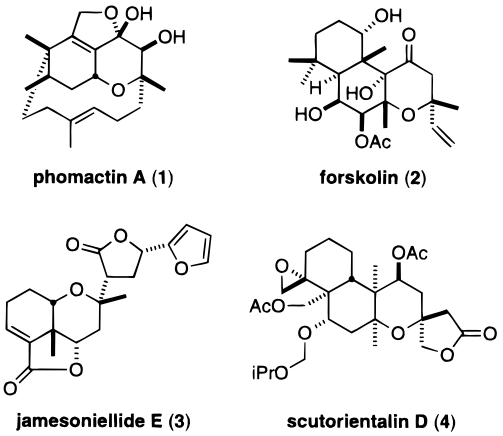

Figure 1.

derivatives of this type react readily with electron-rich dienes to provide highly functionalized 1-oxadecalone derivatives (Table 1).

We first examined the reaction of the 5-carbethoxy dihydropyrone derivative **5a** with the *tert*-butyldimethylsilyl derivative of Danishefsky's diene **8** (entry 1). Here, Diels−Alder reaction occurs in refluxing toluene to provide the Diels−Alder adduct in 85% yield as a ca. 6:1 mixture of diastereomers.[10,11] In this case, stereochemistry is of little consequence as the C5 stereocenter is subsequently destroyed. Here, direct hydrolysis of the enol ether is complicated by the facile degradation of the product 1-oxadecalone (**7**, W = CO_2Et, X = H) to give ethyl *p*-hydroxybenzoate. Presumably, formation of this contaminant results from hydration of the C4 ketone (e.g., **7**), with subsequent retro-Claisen reaction, elimination, and aromatization of the carbocyclic ring (Figure 2).[12] This process can be cleanly circumvented by reduction at C4 prior to hydrolysis. Though in certain cases derivatives of this type can be isolated with the C4 ketone intact (entries 3, 4, and 7), in general, 1-oxadecalone derivatives (**7**) that lack a substituent at C5 are subject to this degredative aromatization pathway. Upon incorporation of added functionality at C1 of the diene (and hence at C5 of the 1-oxadecalone), direct hydrolysis of the initially formed enol ethers occurs to give a stable product (entries 8−14).[13]

A variety of functionalized 1-oxadecalones are accessible by this method. As anticipated, a number of different electron-withdrawing substituents can be utilized to activate the dienophile toward Diels−Alder reaction. In addition to the 5-carbethoxy derivative **5a**, 5-cyano- (**5b**), 5-phenyl sulfone- (**5c**), and 5-acetyl-2,3-dihydro-4-pyrones (**5d**) participate readily in the cycloaddition reaction. Though best results are obtained in the reactions of the dihydropyrones with unhindered, highly oxygenated dienes,[14] even 1,1-

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(1) Sugano, M.; Sato, A.; Iijima, Y.; Oshima, T.; Furuya, K.; Kuwano, H.; Hata, T.; Hanzawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 5463. For a synthetic approach to the tricyclic furanochroman core of phomactin A, see: Foote, K. M.; Hayes, C. J.; Pattenden, G. *Tetrahedron Lett.* **1996**, *37*, 275.

(2) Bhat, J. V.; Bajwa, B. S.; Dornauer, H.; de Souza, N. J.; Fehlhaber, H. W. *Tetrahedron Lett.* **1977**, *33*, 1669. (b) Ueno, Y. *Trichothecenes—Chemical, Biological, and Toxicological Aspects*; Elsevier: Amsterdam, 1983; Vol. 4.

(3) Tazaki, H.; Zapp, J.; Becker, H. *Phytochemistry* **1995**, *39*, 859.

(4) Malakov, P. Y.; Papanov, G. Y.; Spassov, S. L. *Phytochemistry* **1997**, *44*, 121.

(5) For the synthesis of simple 1-oxadecalins see: (a) Anzalone, L.; Hirsch, J. A. *J. Org. Chem.* **1985**, *50*, 2608. (b) Dolmazon, R.; Gelin, S. *J. Org. Chem.* **1984**, *49*, 4003.

(6) (a) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *43*, 3075. (b) Sain, B.; Prajapati, D.; Mahajan, A. R.; Sandhu, J. S. *Bull. Chem. Soc. Fr.* **1994**, *131*, 313. (c) Ohkata, K.; Kubo, T.; Miyamoto, K.; Ono, M.; Yamamoto, J.; Akiba, K. *Heterocycles* **1994**, *38*, 1483. (d) Hsung, R. P. *J. Org. Chem.* **1997**, *62*, 7904.

(7) Groundwater, P. W.; Hibbs, D. E.; Hursthouse, M. B.; Nyerges, M. *J. Chem. Soc., Perkin Trans. 1* **1997**, 163.

(8) Totah, N. I.; Chen, D. *Tetrahedron Lett.* **1998**, *39*, 213.

(9) To date we have been unable to identify conditions under which the parent 2,3-dihydro-2,2-dimethyl-4-pyranone will react, even with highly activated dienes.

(10) The stereochemistry of the major diastereomer is tentatively assigned as that bearing an α-methoxy function at C5 (cf. **6**). This stereochemical assignment is based on the observation of long-range coupling between protons on C5 and C8a of the major Diels−Alder adduct.

(11) Though 85% represents the yield of the purified Diels−Alder adduct, routinely these compounds are utilized in subsequent transformations without purification.

(12) Ethyl *p*-hydroxybenzoate can be isolated cleanly from the reaction mixture.

(13) Presumably, the presence of a substituent at C5 impedes hydration of the C4 ketone due to an increase in steric hindrance.

(14) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753.

(15) Under thermal conditions, hydrolysis of the diene predominates, particularly at elevated temperatures. Cf. Rathke, M. W.; Sullivan, D. F. *Synth. Commun.* **1973**, 67.

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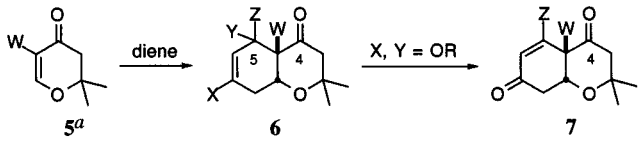
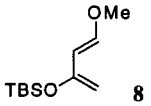
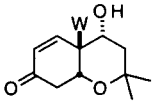
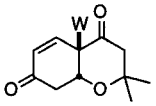
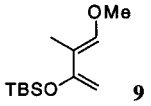
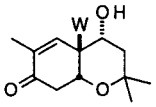
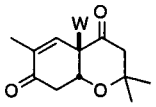
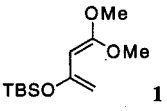
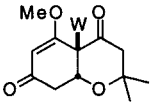
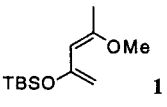
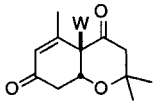
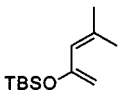
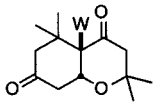
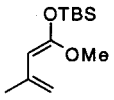
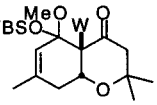
Table 1. Synthesis of 1-Oxadecalones



5[a] 6 7

entry	diene	reaction conditions	product		yield[b]
1	 8	**5a**, 110°C, toluene, 48h; $NaBH_4$; Bu_4NF		**14a** W = CO_2Et	54%
2		**5b**, 110°C, toluene, 48h; $NaBH_4$; pTsOH		**14b** W = CN	48%
3	8	**5c**, 110°C, toluene, 48h; pTsOH		**14c** W = SO_2Ph	64%
4		**5d**, 110°C, toluene, 24h; 10% HF, CH_3CN		**14d** W = $COCH_3$	72%
5	 9	**5a**, 110°C, toluene, 28h; $NaBH_4$; pTsOH		**15a** W = CO_2Et	56%
6		**5b**, 110°C, toluene, 36h; $NaBH_4$; pTsOH		**15b** W = CN	68%
7	9	**5c**, 110°C, toluene, 24h; 10% HF, CH_3CN		**15c** W = SO_2Ph	78%
8	 10	**5a**, 25°C, neat, 8h; pTsOH		**16a** W = CO_2Et	85%
9		**5b**, 25°C, benzene, 20h; pTsOH		**16b** W = CN	75%
10		**5c**, 25°C, benzene, 20h; H_2, Pd/C[c]		**16c** W = SO_2Ph	60%
11		**5d**, 25°C, benzene, 36h; 10% HF, CH_3CN		**16d** W = $COCH_3$	56%
12	 11	**5a**, 110°C, toluene, 40h; 10% HF, CH_3CN		**17a** W = CO_2Et	48%
13		**5b**, 110°C, toluene, 60h; 10% HF, CH_3CN		**17b** W = CN	40%
14	 12	**5b**, 110°C, toluene, 72h; 10% HF, CH_3CN		**18a** W = CN	38%
15	 13	**5b**, Et_2AlCl (0.2 eq), CH_2Cl_2, -78°C - RT		**19a** W = CN	83%

[a] **5a** W = CO_2Et; **5b** W = CN; **5c** W = SO_2Ph; **5d** W = $COCH_3$; [b] Isolated yields based on starting dihydropyrone; [c] Under these conditions, competing reduction of the product enone is not observed.

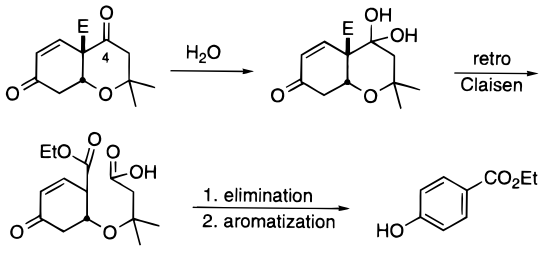


Figure 2.

disubstituted dienes such as **11** and **12** (entries 12−14) react to give reasonable yields of 1-oxadecalone derivatives in the two-step Diels−Alder/hydrolysis sequence.

Conversely, 1-(*tert*-butyldimethylsilyloxy)-1-methoxy-3-methyl-1,3-butadiene **13** reacts only slowly with dihydropyrones of these types, and little of the cycloadduct is observed under thermal conditions, even in the presence of a large excess of diene.[15] However, in the presence of a catalytic amount of Lewis acid, Diels−Alder reaction of the cyano derivative **5a** occurs readily to provide the desired Diels−Alder adduct as a 2.3:1 mixture of diastereomers.

In conclusion, we have demonstrated for the first time that 2,3-dihydro-4-pyrones can serve effectively as dienophiles in the Diels−Alder reaction. In this way, a variety of highly functionalized 1-oxadecalins are readily available under relatively mild conditions. Furthermore, by modifying the electron-withdrawing group at C5 of the dihydropyrone a variety of functionalities can be incorporated at the ring junction. This ability should allow for added flexibility in the synthesis of more complex substrates. Further studies aimed at expanding the scope and application of this method are currently underway. These results will be reported in due course.

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Supporting Information Available: Experimental procedures, compound characterization data, and copies of spectra for compounds **14**−**19**.

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