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Oxabicyclo[3.2.1]octane Derivatives as Highly Reactive Dienophiles: Synthesis of Bicyclo[5.*n*.0] Systems

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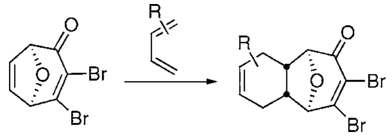
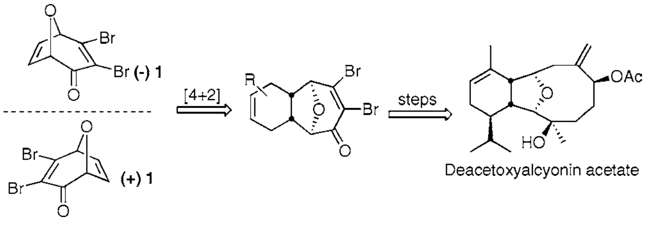
ABSTRACT



We have developed highly versatile, homochiral oxabicyclo[3.2.1]octadiene building blocks for the synthesis of natural products. We have found that these bridged alkenes undergo exceptionally facile Diels–Alder reactions and react faster than several well studied bicyclo[2.2.1]heptene dienophiles. The reaction proceeds with high levels of stereochemical control and in very good to excellent yields, providing access to bicyclo[5.4.0]undecane and bicyclo[5.3.0]decane systems. This reactivity is attributed to strain and homoconjugation effects.

Over the past several years, we have developed both racemic and homochiral oxabicyclo[3.2.1]octadiene synthons from the cyclocondensation products of furan and tetrabromo- or tetrachlorocyclopropene.[1] A particularly versatile derivative is the dibromoenone **1**, which is available in either enantiomeric form in just three steps from furan[2] and is currently being utilized in an approach to deacetoxyalcyonin acetate (Scheme 1).

Scheme 1. Bicyclic Synthons for Eunicellin Synthesis



Our approach called for an initial four-carbon annulation across the two-carbon bridge to produce a key bicyclo[5.4.0]undecane intermediate. This will be followed by a three-carbon annulation across the dibromoenone and cleavage of the intracyclic olefin to unveil the oxabridged cyclodecane ring of deacetoxyalcyonin acetate.[4] Prior studies have shown that the dibromoenone moiety is amenable to a wide range of transformations, including substitutions and cross-coupling reactions that form the basis for annulation of this bridge.[3] In contrast to this portion of the bicyclic synthon, little was known about the ability to effect annulation across the unsaturated two-carbon bridge. Although unfunctionalized, it has been appreciated that the strain inherent in bridged bicyclic compounds (notably norbornene) render the unactivated olefin relatively reactive. The use of a Diels−Alder reaction to effect annulation was attractive since it would directly produce the six-membered A-ring, while the constrained nature of **1** was expected to impart high levels of

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(1) (a) Oruganty, R. S.; Wright, D. L.; Battiste, M. A.; Abboud, K. A. *Org. Lett.* **2002**, *4*, 1997. (b) Orugunty R. S.; Ghiviriga, I.; Abboud, K.; Battiste, M. A.; Wright, D. L. *J. Org. Chem.* **2004**, *69*, 570. (c) Batson, W. A.; Abboud, K. A.; Battiste, M. A.; Wright, D. L. *Tetrahedron Lett.* **2004**, *45*, 2093.

(2) Pelphrey, P. M.; Abboud, K. A.; Wright, D. L. *J. Org. Chem.* **2004**, 6931.

(3) Orugunty R. S.; Wright, D. L.; Battiste, M. A.; Helmich, R. J.; Abboud, K. *J. Org. Chem.* **2004**, *69*, 406.

(4) Total synthesis: (a) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033. (b) Molander, G. A.; St. Jean, D, J.; Haas, J. *J. Am. Chem. Soc.* **2004**, *126*, 1642.

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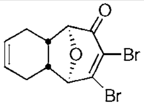
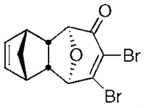
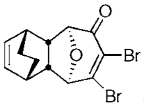
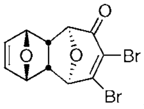
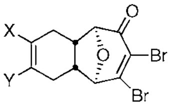
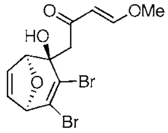
Table 1. Diels−Alder Reactions of Enone **1**

entry	diene	conditions[a]	product	yield
1	butadiene[b]	135° C, 30 h	 **2**	80%
2	cyclopentadiene	25° C, 24 h	 **3**	97%
3	cyclohexadiene	130° C, 30 h	 **4**	95%
4	furan	100° C, 5 d	 **5**	60%
5	isoprene	110° C, 5 d	 **6a** X=Me, Y=H **6b** X=H, Y=Me	60%[c]
6	1-methoxy-3-trimethylsiloxy butadiene	80° C	 **7**	N/A

[a] All reactions were run in toluene in a sealed tube. [b] Generated from sulfolene. [c] Combined yield of **6a/b** in a ~1:1 ratio.

facial selectivity on the cycloaddition. Diels−Alder reactions with oxabicyclo[3.2.1]octenes[5] have remained virtually unexplored in contrast to oxabicyclo[2.2.1]heptene systems,[6] and it was unclear if compounds such as **1** could be forced to participate in a Diels−Alder reaction. A series of cycloaddition reactions between **1** and various dienes were examined to ascertain if this process could be employed in a synthetically useful manner (Table 1).

Gratifyingly, it was found that **1** is a reactive dienophile and condensed with both cyclic and acyclic dienes to produce the corresponding cycloadducts (**2**−**5**) in very good to excellent yields and as single diastereomers. No products arising from reaction with the dibromoenone moiety were observed. In all cases, the diene had approached the dienophile from the more accessible *exo*-face of the oxabicyclic derivative. This stereochemical outcome could be easily determined by the coupling constants between the adjacent bridgehead and angular protons. X-ray analysis of adducts **4** and **5** verified this assignment and revealed that the approach of the diene had occurred in the *endo* mode. This was surprising for furan adduct **5**, which was expected to equilibrate at high temperatures to the *exo*-adduct. This may reflect a repulsive interaction between lone pairs when the oxabridges are in a syn relationship.[7]

Reaction with an unsymmetrical diene (isoprene) showed little regiochemical bias, producing adducts **6a**/**b** in almost equal amounts. Attempts to use the more highly polarized Danishefsky diene led only to the product of aldol condensation **7**, albeit in relatively low yields.

The facility of these cycloaddition reactions with dienes of moderate reactivity such as butadiene and cyclohexadiene was noteworthy, as the bicyclo[3.2.1]octene derivatives are less strained than the typical norbornene-type systems. To gauge the relative reactivity of **1** with classic bridged dienophiles, a series of competition experiments was conducted whereby an equivalent amount of **1** and another dienophile, **8**−**12**, were allowed to compete for a single equivalent of cyclopentadiene (Figure 1).

Olefin **1** was shown to be more reactive than either the carbon- or oxygen-bridged [2.2.1]heptene systems **8** and **9**

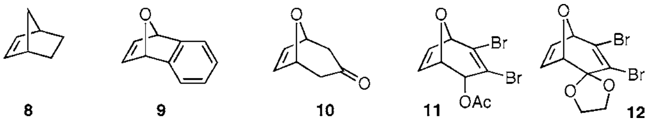


Figure 1. Bridged dienes for competition studies.

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(5) We are aware of one inter- (Eiden, F.; Kainz, A.; Gebhard, R. *Arch. Pharm.* **1992**, *235*, 77) and one intramolecular example (Pyne, S. G.; Spellmeyer, D. C.; Chen, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1982**, *104*, 5728).

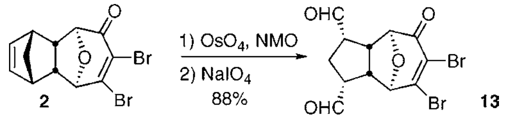
(6) Vogel, P.; Cosey, J.; Plumet, J.; Arjona, O. *Tetrahedron* **1999**, *55*, 13521.

as well as the popular oxabicyclo[3.2.1]octane derivative **10** derived from oxyallylcation cycloaddition chemistry. In all cases, no cycloaddition products from these other alkenes were detected. In fact, olefin **10** was a relatively poor dienophile toward cyclopentadiene and gave only modest yields of the adduct after prolonged heating. The basis of the exceptional reactivity of **1** was thought to be related to the increase in ring strain by the inclusion of 5 sp^2 centers in the carbocylic framework and the proximity of the electron-withdrawing ketone, which can lower the HOMO of the olefin through homoconjugation.[8] The more remote carbonyl in **10** has less opportunity to withdraw electron density from the alkene, which may relate to its lower reactivity in the [4 + 2] reaction. To examine the role of the proximal carbonyl group in **1**, the corresponding acetate **11**[9] and ketal **12**[3] were studied.

In a competition reaction between **1** and acetate **11** or ketal **12** for cyclopentadiene, only the product derived from Diels–Alder reaction of **1** was observed. Although the reduction of the carbonyl group eliminates the ability to interact with the distal olefin through homoconjugation, it also alleviates some of the ring-strain in the system ($sp^2 \rightarrow sp^3$), which would also be expected to attenuate the reactivity of the alkene.

The facility of Diels–Alder reactions with these chiral synthons permits access to a range of bicyclic building blocks. Bicyclo[5.4.0]undecane systems are available directly from the cycloaddition with a variety of dienes. Alternatively, bicyclo[5.3.0]decane (perhydroazulene) systems common to many natural products such as the guanacastepenes[10] can be realized through oxidative cleavage of the cyclopentadiene adduct **2** (Scheme 2).

Scheme 2. Oxidative Cleavage of a Cyclopentadiene Adduct



Two-step cleavage of adduct **2** through an initial osmylation followed by periodate cleavage produced the dialdehyde **13** in good overall yield. Typical one-step cleavage conditions ($OsO_4/NaIO_4$) or ozonolysis resulted in extensive decomposition of the dialdehyde.[11]

The high reactivity of the readily available enone **1** toward a variety of dienes allows straightforward access to bicyclo[5.4.0]undecane and bicyclo[5.3.0]decane systems that are common core structures in a variety of natural products. The carbonyl group in the bicyclic structure is key to this high level of reactivity. Application of these compounds in the synthesis of natural products is ongoing and will be reported in due course.

Acknowledgment. The authors would like to thank the National Science Foundation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and Dartmouth College for support of this work.

Supporting Information Available: Experimental procedures and characterization data for compounds **2**–**6** and **13** and X-ray structures for cycloadducts **4** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] Black, K. A.; Vogel, P. *J. Org. Chem*. **1986**, *51*, 5341.

[9] Generated by acylation of the known *endo*-alcohol; see ref 3.

[10] (a) Brady, S. F.; Singh, M. P.; Janso, J. E.; Clardy, S. *J. Am. Chem. Soc.* **2000**, *122*, 2116–7 (b) Singh, M. P.; Janso, J. E.; Luckman, S. W.; Brady, S. F.; Clardy, J.; Greenstein, M.; Maiese, W. M. *J. Antibiot.* **2000**, *53*, 256–61.

[11] Lee, M.; Ikeda, I.; Kawabe, T.; Mori, S.; Kanematsu, K. *J. Org. Chem*. **1996**, *61*, 3406.