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An Interesting Issue of Diels–Alder Selectivity Discovered En Route to 11-*O*-Debenzoyltashironin

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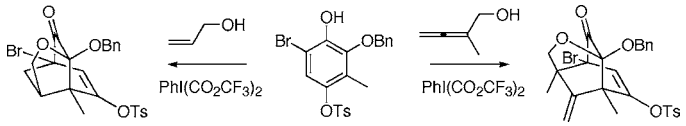
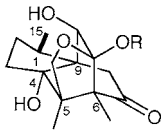
ABSTRACT



The hypervalent iodine-mediated oxidative dearomatization/Diels–Alder cascade was examined in the context of the natural product 11-*O*-debenzoyltashironin. Interestingly, the regioselectivity of the Diels–Alder reaction can be completely switched by changing the dienophile. Trapping of allyl alcohols during the oxidative dearomatization gives rise to the five-membered acetal, while trapping of allenyl alcohols results in the six-membered acetal.

In the context of our ongoing interest in the synthesis and biological evaluation of neurotrophically active small molecules,[1] we recently launched an effort directed toward the total synthesis of the anistatin-related natural product, 11-*O*-debenzoyltashironin (**1**) (Figure 1). Isolated from the Eastern Asian *Illicium merrillianum*, **1** has been shown to promote neurite outgrowth at concentrations as low as 0.1 μmol.[2] Interestingly, its benzoylated congener, tashironin (**2**), exhibits no observable neurotrophic activity.[3] Aside from our anticipation that **1** is a potentially valuable lead candidate in the development of a neurotrophic agent, we were particularly drawn to issues of chemical interest in attempting to synthesize the highly oxygenated, densely functionalized core structure of 11-*O*-debenzoyltashironin.



R = H: 11-*O*-Debenzoyltashironin (**1**)
R = Bz: Tashironin (**2**)

Figure 1. 11-*O*-Debenzoyltashironin (**1**) and tashironin (**2**).

The initial task would be that of assembling a [2.2.2] bicyclic core, appropriately functionalized for installation of the remaining structural features of the molecule. We describe herein our investigations into an oxidative dearomatization-Diels−Alder cascade strategy to allow for the assembly of the core structure.

The Tamura−Pelter oxidation,[4] originally conceived of as a means of access to *p*-quinone dialkyl monoketals through oxidative dearomatization of phenols in methanol, was further advanced by the pioneering work of Liao to include intermolecular trapping by various allylic alcohols with subsequent Diels−Alder cyclization.[5] Our strategy for the assembly of the tashironin core, outlined in Scheme 1, envisioned recourse

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(1) For a recent account of our laboratory's involvement in this area, see: Wilson, R. M.; Danishefsky, S. J. *Acc. Chem. Res.* **2006**, *39*, 539.

(2) Huang, J. M.; Yokoyama, R.; Yang, C. S.; Fukuyama, Y. *J. Nat. Prod.* **2001**, *64*, 428.

(3) Fukuyama, Y.; Shida, N.; Kodama, M. *Tetrahedron Lett.* **1995**, *36*, 583.

(4) (a) Tamura, Y.; Yakura, T.; Haruta, J. I.; Kita, Y. *J. Org. Chem.* **1987**, *52*, 3927. (b) Pelter, A.; Elgendy, S. *Tetrahedron Lett.* **1988**, *29*, 677.

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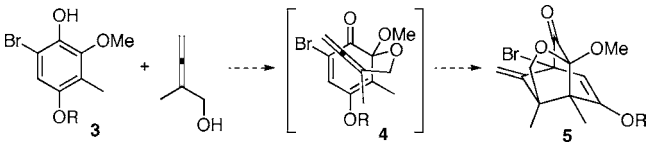
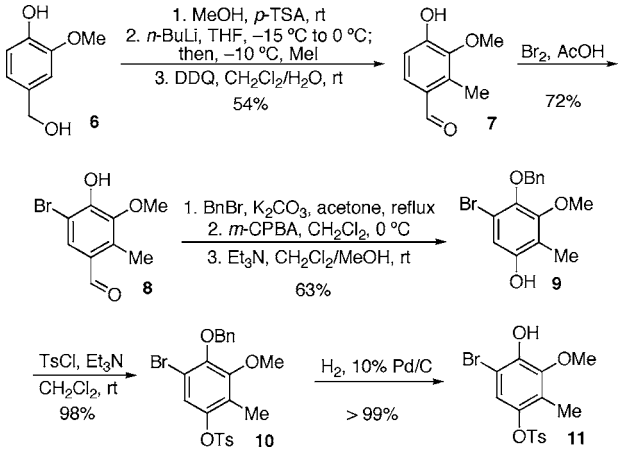
Scheme 1. Proposed Oxidative Dearomatization−Diels−Alder Cascade



to this powerful, complexity building sequence. It was anticipated that intermolecular oxidative dearomatization of **3**, in the presence of an allenyl alcohol, would provide the *o*-quinone intermediate, **4**. We hoped that the latter would undergo spontaneous intramolecular Diels−Alder cyclization to provide the tashironin core, **5**. This rapidly assembled complex intermediate would be equipped with the pendant functionality required for the completion of the synthesis of the natural product.

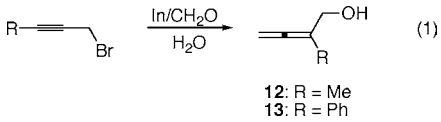
The synthesis of the requisite aromatic substrate, **11**, commenced with vanillyl alcohol (**6**). Treatment of the latter with a catalytic amount of tosyl acid in methanol served to methoxylate the presumed transient *p*-quinone methide intermediate (Scheme 2). Installation of the aromatic methyl

Scheme 2. Synthesis of Phenol **11**



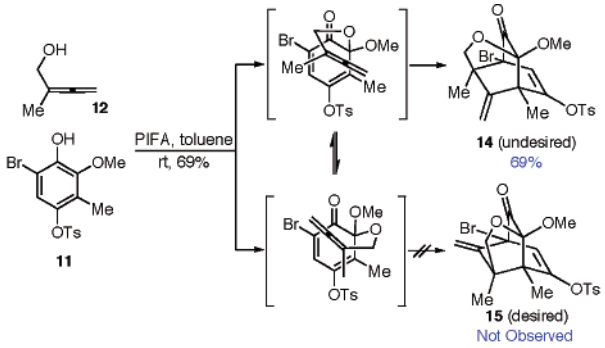
group at the more hindered position was achieved through chelation-controlled aryl lithiation with subsequent alkylation. DDQ-mediated oxidation afforded **7** in 54% overall yield. Hydroxyl-directed bromination of **7** provided phenol **8**. Benzylation followed by *m*-CPBA-mediated Baeyer−Villiger oxidation generated an intermediate formate, which upon hydrolysis gave rise to phenol **9** (63% yield over three steps). Finally, tosylation followed by benzyl deprotection yielded the desired substrate **11** in 98% yield.

Allenyl alcohols **12** and **13** were prepared from the corresponding propargyl halides, as shown in eq 1.[6]



12: R = Me
13: R = Ph

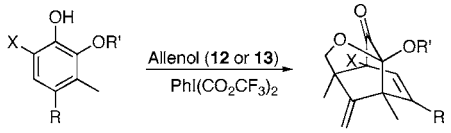
Scheme 3. Oxidative Dearomatization−IMDA of **11**



The successful implementation of our strategy would require intermolecular trapping of the allenyl alcohol through oxidative dearomatization. This step would be followed by intramolecular Diels−Alder reaction with the internal olefin of the allenol. In contemplating this approach, we were aware of potential issues of regioselectivity in the Diels−Alder reaction.

In the event, when phenol **11** was combined with PIFA and an excess of allenyl alcohol **12**, a single Diels−Alder product was observed. It was shown to be the undesired acetal product **14** rather than **15** (which would have cor-

Table 1. Allenyl Alcohol Diels−Alder Reaction



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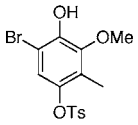
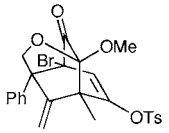
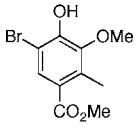
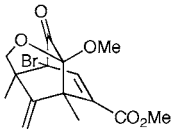
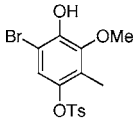
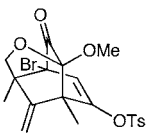
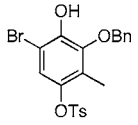
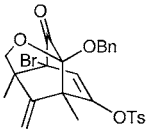
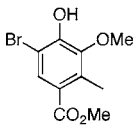
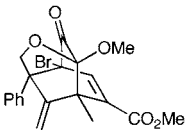
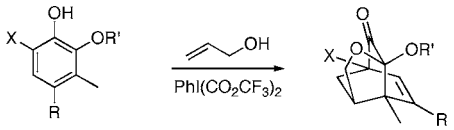
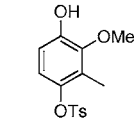
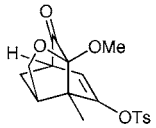
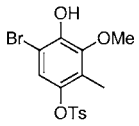
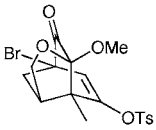
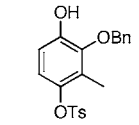
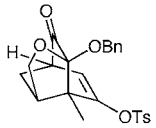
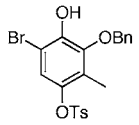
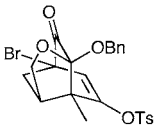
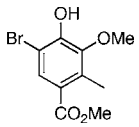
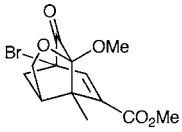
1		**13**		45%
2		**12**		49%
3		**12**		69%
4		**12**		44%
5		**13**		50%

Table 2. Allyl Alcohol Diels−Alder Reaction



entry	phenol	product	yield
1			41%
2			44%
3			58%
4			56%
5			58%

responded to a possible pre-tashironin intermediate) (Scheme 3). The 6-membered acetal could not, however, be exploited toward reaching tashironin.

Thus, we probed the scope of this undesired pathway by investigating the consequences which perturbations of the aromatic ring substituents might have on the regiochemical outcome of the IMDA reaction with allenyl dienophiles. Substrates were prepared in which the tosyl ester was replaced with a methyl ester group (Table 1, entries 2 and 5) and the methyl ether was replaced with a benzyl ether (Table 1, entry 4). In practice, reaction of each of these modified substrates with allenol **12** provided the 6-membered acetal IMDA adduct. When allenyl alcohol **13** was used as the dienophilic coupling partner with phenol **11** (Table 1, entry 1), a crystalline product was obtained. X-ray analysis of the compound revealed unambiguously the 6-membered acetal product.[7]

We sought to explore the outcome of reactions with simpler dienophiles. Interestingly, by changing the dienophile from an allenyl to an allyl system, the direction of the reactions was completely reversed and only the 5-membered acetal could be detected in the latter case (Table 2). As with the allenyl alcohols, modifications of the aromatic ring system did not alter the sense of the Diels−Alder reaction (Table 2).

With the benefit of retrospection, an accounting of the dramatic differences in the results in Tables 1 and 2 can be offered. It seems likely that, from a perspective of steric strain in the product (and of the transition state leading to it), the formation of the 5-membered acetal would be preferred over the 6-membered product, with its additional torquing of the acetal carbon. However, in the allene cases there is a strong preference for initial partial bond formation between the unique sp carbon of the dienophile with C_4 of the dienone. In this way, radicaloid character in the transition state is supported by the tosylate at C_3 and the bromine at C_1, as well as its connected ketone. Given the orienting affinity between C_4 and the sp carbon, the formation of Table 1 products is dictated.

In conclusion, hypervalent iodine-mediated oxidative dearomatization was used to form high energy [4 + 2] precursor systems that readily undergo intramolecular Diels−Alder reaction (Figure 2). Highly substituted, unactivated

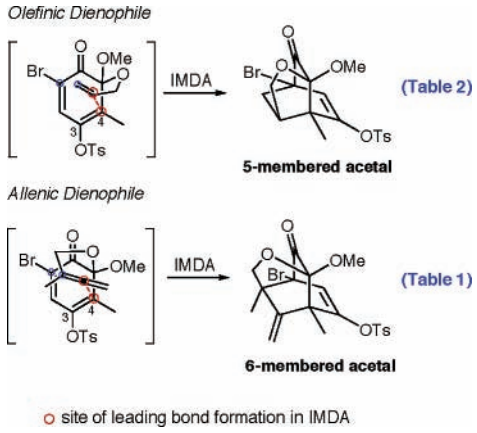


Figure 2. IMDA reactions of allenic and olefinic intermediates.

dienes are used in the reaction to produce complex Diels−Alder adducts. Additionally, the regioselectivity of cyclization can be controlled by judicious choice of dienophile. Applications of these findings are being pursued.

Acknowledgment. Support for this research was provided by the National Institutes of Health (HL25848).

Supporting Information Available: Experimental procedures and physical data for compounds **6**−**14** and Diels−Alder cycloadducts. This material is available free of charge via the Internet at http://pubs.acs.org.

OL062067I

(5) Liao, C. C.; Peddinti, R. K. *Acc. Chem. Res.* **2002**, *35*, 856 and references cited therein.

(6) Isaac, M. B.; Chan, T-H. *J. Chem. Soc., Chem. Commun.* **1995**, 1003.

(7) Crystallographic data (excluding structural data) for the cycloaddition product in Table 1, entry 1, have been deposited with the Cambridge Crystallographic Data Centre (CCDC as Deposition No. CCDC 61734).