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Tandem Hetero Diels–Alder Reaction: Synthesis of Oxygenated Macrocycles

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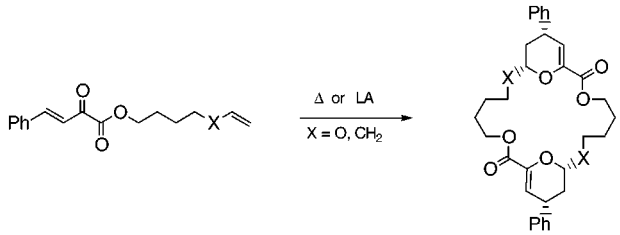
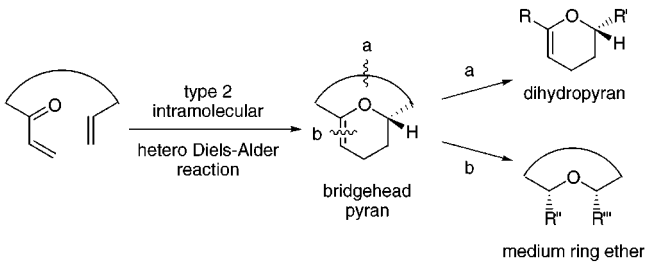
ABSTRACT



C2-symmetric, oxygenated macrocycles have been synthesized from simple acyclic precursors in a single step by a tandem hetero Diels–Alder reaction. Thermolysis and Lewis acid catalysis can effect this novel transformation. The tandem reaction product is formed in preference to the intramolecular cycloaddition product, and an explanation for this result is proposed.

We have been exploring heteroatom variants of the type 2 intramolecular Diels−Alder (IMDA) reaction.[1] If an α,β-unsaturated ketone is used as the 4π component in the cycloaddition reaction, the product formed is a bridgehead pyran (Scheme 1). The bicyclic pyran can be functionalized

Scheme 1



by cleaving the tether that spans the dihydropyran, which would lead to the synthesis of a substituted dihydropyran (path a). Alternatively, functionalization of the bridgehead olefin[2] could provide an entry into α,α′-*cis*-disubstituted medium ring ethers (path b).

The intermolecular hetero Diels−Alder reactions of 2-substituted-1-oxo-butadienes are facilitated by electron-withdrawing groups.[3] Electron-withdrawing groups have been used at the 2, 3, and 4 positions of the heterodiene, with the most success realized with activation at positions 2 and 3. Relevant examples include the work of Sera,[4] Evans,[5] and Jorgensen.[6]

Our studies of the type 2 intramolecular hetero Diels−Alder (IMHDA) reaction have led to the discovery of a novel reaction pathway, the tandem hetero Diels−Alder reaction.

(1) For examples of type 2 intramolecular nitroso Diels−Alder reactions, see: Sparks, S. M.; Vargas, J. D.; Shea, K. J. *Org. Lett.* **2000**, *2*, 1473.

(2) (a) Shea, K. J. *Tetrahedron* **1980**, 36, 1683. (b) Warner, P. M. *Chem. Rev.* **1989**, *89*, 1067.

(3) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Pergamon: Oxford, 1987; Chapter 7.

(4) Sera, A.; Ohara, M.; Yamada, H.; Egashira, E.; Ueda, N.; Setsune, J. *Chem. Lett.* **1990**, 2043.

(5) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635.

(6) Thorhauge, J.; Johannsen, M.; Jorgensen, K. A. *Angew. Chem., Int. Ed., Engl.* **1998**, *37*, 2404.

(7) Stetcher, E. D.; Ryder, H. F. *J. Am. Chem. Soc.* **1952**, *74*, 4392.

(8) (a) Schmidt, R. R.; Maier, M. *Tetrahedron Lett.* **1985**, *26*, 2065. (b) Tietze, L. F.; Hubsch, T.; Voss, E.; Buback, M.; Trost, W. *J. Am. Chem. Soc.* **1988**, *110*, 4065. (c) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 3373.

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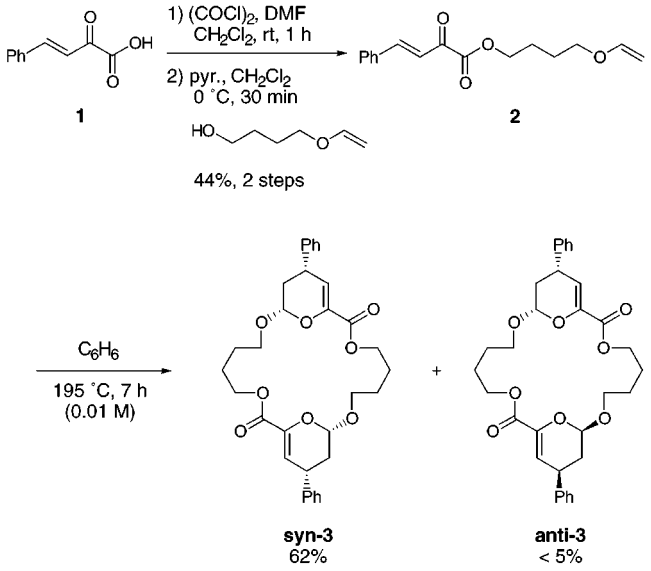
Examination of the type 2 IMHDA reaction commenced with the synthesis of ester activated heterodiene **2** (Scheme 2). α-Keto acid **1**[7] was converted to ester **2** using standard

Scheme 2



conditions. Thermolysis of α-keto ester **2** did not lead to the expected type 2 IMHDA product, but instead the major product had a mass exactly double the expected product.

We tentatively assigned the structure of the major product as macrocycle **3** and proposed a sequential reaction pathway to account for its formation: the tandem hetero Diels−Alder reaction. We believed both cycloadditions would occur through the *endo* transition state to produce the *cis* stereochemistry at both dihydropyrans.[8] It was unclear if the relative stereochemistry of the two bridged ring systems could be controlled in the macrocyclization. An X-ray crystal structure confirmed the connectivity and the all-*cis* relative stereochemistry of the major product, compound ***syn*-3** (Figure 1).

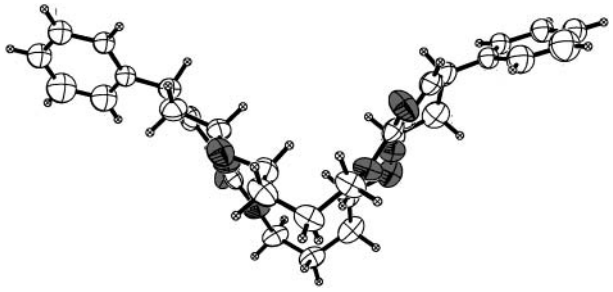


Figure 1. Molecular structure of macrocycle ***syn*-3**. The oxygens of the 20-membered macrocycle are darkened for clarity.

A minor product ***anti*-3** (<5%) was also isolated from the reaction. X-ray crystallography established the anti relationship between the two *cis*-dihydropyran rings of this product (Figure 2). Both cycloadditions are stereoselective. In addition, the second cycloaddition exhibits a 12:1 selectivity for the syn macrocycle. We do not at present have a compelling explanation for this observation.

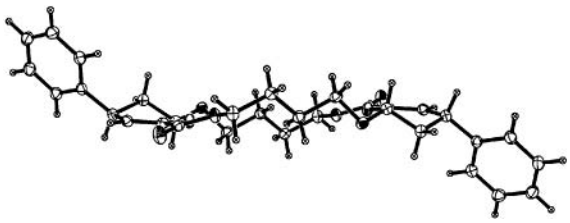
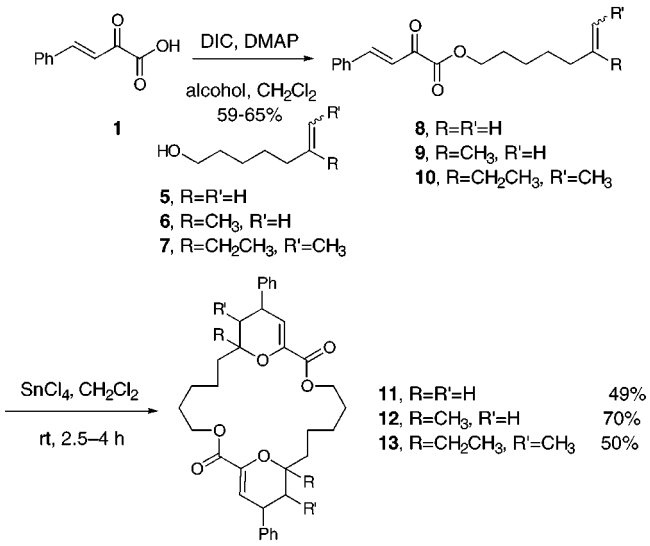


Figure 2. Molecular structure of minor product ***anti*-3** from the thermolysis of α-keto ester **2**.

Intrigued by these findings, we decided to investigate the synthesis of other crown-ether-like compounds using the tandem hetero Diels−Alder reaction. Lewis acid catalysis and alkyl dienophiles were employed to examine the scope of the reaction. α-Keto acid **1** was coupled with primary alcohols **5**−**7**[9] to provide α-keto esters **8**−**10** (Scheme 3).

Scheme 3



A variety of Lewis acids were screened. $SnCl_4$ was found to be superior for the tandem hetero Diels−Alder cyclization of α-keto esters **8**−**10** to produce macrocycles **11**−**13**. The connectivity of compounds **11**−**13** was determined by ^1H and ^{13}C correlation to tricycle ***syn*-3** and mass spectral analysis. In each case, the dimer was the only product produced. Efforts are underway to grow crystals suitable for X-ray analysis to permit assignment of the overall relative stereochemistry of the cycloadducts. Examination of the crude reaction mixtures indicates two stereomeric products were formed, similar to that found in the thermolysis of **2**.

The mild reaction conditions allow increased functionalization of the cycloaddition precursors, making analogue synthesis a reality.

The preceding results can be understood in terms of the reactivity of the corresponding bimolecular reactions. In the intermolecular hetero Diels−Alder reaction of 2-activated enone dienes with both activated and unactivated dienophiles, excellent regioselectivity is observed (Figure 3). FMO

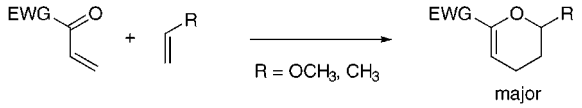


Figure 3. Regioselectivity of the intermolecular hetero Diels−Alder reaction of 2-activated enone dienes with activated and unactivated dienophiles.

analysis has been used to explain the regiochemical outcome of the cycloaddition.[10]

Hetero Diels−Alder reactions of 1-oxobutadienes are often stereoselective. Under thermal conditions, the *endo* mode of cycloaddition typically dominates, producing the 4,6-*cis* dihydropyran product.[8] Conversely, Lewis acid catalysis ($SnCl_4$) of similar reactions leads to the 4,6-*trans* product, which arises from the *exo* mode of cycloaddition.[4] The tin complex is believed to be octahedral, and this complex blocks the dienophile from approaching the heterodiene through the traditional *endo* mode; therefore, the *exo* cycloadduct is formed.

We can draw upon the preceding to explain the observed regiochemical and stereochemical outcome of the thermolysis of α-keto ester **2,** while conformational considerations can be used to account for the absence of the type 2 IMHDA product. It is known that the α,*β*-unsaturated α-keto esters prefer to have the *π*-system coplanar (Figure 4).[11] Also, it

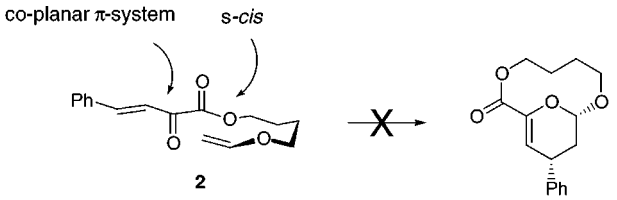
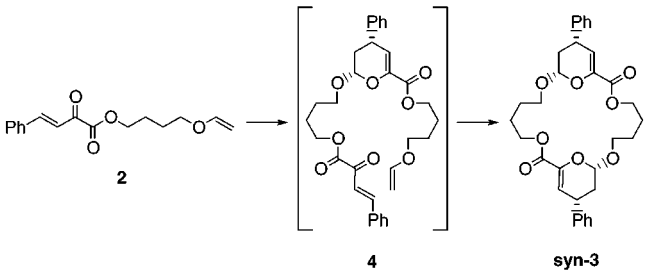


Figure 4. Conformational restrictions of α-keto ester **2** disfavoring the type 2 IMHDA reaction.

has been documented that esters prefer to reside in an s-*cis* conformation to the s-*trans* orientation. With these conformational preferences in place, the tether is effectively shortened and the dienophile is unable to approach the hetero diene without the introduction of considerable steric energy; therefore the type 2 IMHDA reaction is not favorable.

Product **3** therefore is formed in a stepwise process: the tandem hetero Diels−Alder reaction (Scheme 4). Initially,

Scheme 4



an *endo* intermolecular hetero Diels−Alder reaction takes place to produce *cis*-substituted dihydropyran intermediate **4**. After the first cycloaddition, conformational restrictions no longer prohibit the intramolecular cyclization. The dilute reaction conditions (0.01 M) favor intramolecular cyclization; therefore, dihydropyran **4** can undergo a hetero Diels−Alder reaction to form macrocycle ***syn*-3**.[12]

In reactions catalyzed by $SnCl_4$, it is believed the Lewis acid coordinates the α-dicarbonyls, forming an octahedral complex, which makes the *endo* cycloaddition mode unfavorable (Figure 5). In addition, the tether is too short to allow

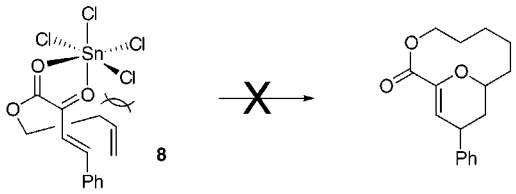


Figure 5. Proposed octahedral complex of the Lewis acid ($SnCl_4$) and α-keto ester **8** disfavoring the type 2 IMHDA reaction.

the dienophile to interact with the heterodiene through the *exo* transition state; therefore, both modes of intramolecular cycloaddition are shut down. Again, the dienophile reacts initially intermolecularly, and the macrocycle is formed by a subsequent intramolecular cycloaddition.

Examination of the type 2 intramolecular hetero Diels−Alder reaction utilizing 2-alkenyl ester-1-oxa-butadienes as the 4*π* components has led to the discovery of a tandem hetero Diels−Alder reaction. In this reaction sequence, highly oxygenated macrocycles can be formed from simple acyclic precursors in a single step under thermal or Lewis acid

(9) Alcohols **6** and **7** were synthesized using the procedure described in Brunel, Y.; Rousseau, G. *Tetrahedron Lett.* **1996**, *37*, 3853.

(10) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; John Wiley and Sons: New York, 1998; pp 141−142.

(11) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; p 619.

(12) In addition, very dilute conditions ($<1 \times 10^{-6}$ M) have been employed attempting to effect the type 2 intramolecular cycloaddition. Even under these conditions, the only product observed was dimer **3**.

catalyzed conditions. We believe this is the first example of a transformation of this type. With the ease of synthesis of the cycloaddition precursors, this chemistry is amenable to analogue synthesis. Studies to determine the cation affinity and specific utility of the macrocycles are currently being conducted.

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Supporting Information Available: X-ray crystallographic data for compounds ***syn*-3** and ***anti*-3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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