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Stereoselective Synthesis of Highly Functionalized 1,5-Oxa-Bridged Cyclooctenes via a 3-Oxidopyrylium–Cyclocypropene Acetal Cycloaddition

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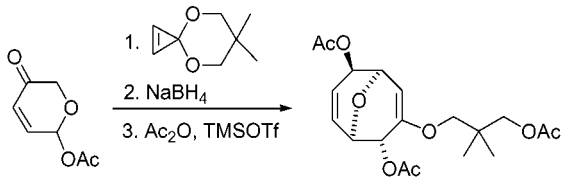
ABSTRACT

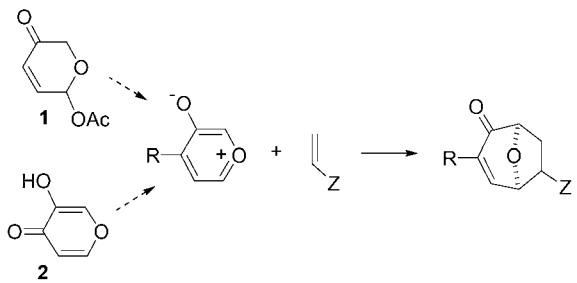


A [5C+2C] oxidopyrylium–cyclopropenone acetal cycloaddition followed by ring opening of the cyclopropane unit of the resulting adduct leads to highly substituted 1,5-oxa-bridged cyclooctenes containing up to four stereocenters. The protocol formally constitutes a [5C+3C] annulation process.

The 3-oxidopyrylium ylide−alkene cycloaddition is a simple, well-established method to rapidly assemble highly functionalized 8-oxabicyclo[3.2.1]octanes from readily available precursors.[1] The most extensively used procedure to generate the required dipoles involves thermolysis or base treatment of 6-acetoxy-3-pyranones such as **1**,[1,2] although other methods based on the elaboration of 3-hydroxy-4-pyrones (**2**) have also been described (Scheme 1).[3]

The oxabicyclic products can be stereoselectively manipulated in a variety of ways and of particular interest are those that unmask the embedded cycloheptane.[4] A variety of activated and strained alkenes have been shown to participate as two-carbon partners in this type of cycloaddition,[1b] but to our knowledge cyclopropenes have not been investigated.[5] Since cyclopropenone acetal **3** is a versatile two- or three-carbon partner in a variety of cycloadditions,[6] we were curious about its behavior when confronted with 3-oxidopyrylium ylides. Herein we show that cyclopropenone

Scheme 1



(1) (a) Katrizky, A. R.; Dennis, N. *Chem. Rev.* **1989**, *89*, 827. (b) Sammes, P. G.; Street, L. J. *Gazz. Chim. Ital.* **1986**, *116*, 106.
(2) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359.
(3) (a) Mascareñas, J. L. In *Advances in Cycloaddition*; Harmata, M., Ed.; JAI Press: Stamford, CT, 1999; Vol. 6, pp 1−54. (b) Mascareñas, J. L.; Rumbo, A.; Castedo, L. *J. Org. Chem.* **1997**, *62*, 8620. (c) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L *J. Org. Chem.* **1999**, *64*, 966. (d) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L *J. Org. Chem.* **2000**, *65*, 2528.
(4) (a) Chiu, P.; Lautens, M. In *Topics in Current Chemistry*; Springer-Verlag: Berlin, Germany, 1997; Vol. 190, p 1. (b) Rodríguez, J. R.; Castedo, L.; Mascareñas, J. L. *Synthesis* **2000**, 980.

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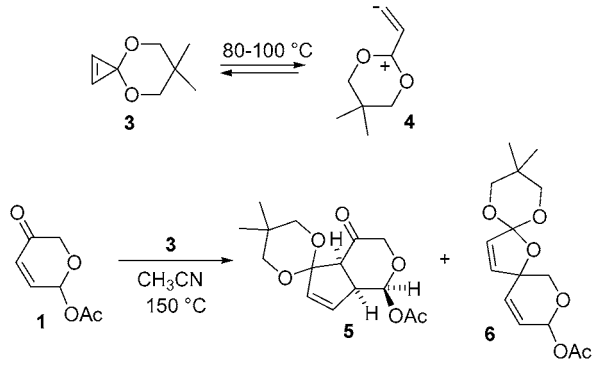
acetal **3** reacts smoothly and efficiently with the pyranulose acetate **1** upon treatment with base to give the expected [5C+2C] cycloadduct. Most importantly, this adduct can be stereoselectively elaborated to give synthetically appealing, highly functionalized oxa-bridged cyclooctanes through an unprecedented cleavage of their cyclopropanone acetal moiety.

Cyclopropenone acetal **3** participates as a three-carbon component in thermal cycloadditions with highly activated alkenes (3+2 annulation) as well as with some particular type of dienes (3+4 annulation).[6] This behavior has been explained in terms of the reversible formation of the singlet π-delocalized vinylcarbene species **4** upon mild heating. The prospect that this intermediate could react with a 3-oxidopyrylium ylide precursor in a (3+5) manner led us to investigate the reaction of acetoxypyranone **1** with **3** under thermal activation. However, heating of a 1:1.2 mixture of **1** and **3** in CH_3CN at 150 °C did not produce the desired cycloadduct, although we did isolate a small amount of the [3+2] annulation products **5** and **6** in a 24% and 11% yield, respectively.[7] Heating at lower temperatures (110 °C) led to the same adducts in similar yields. Although the formation

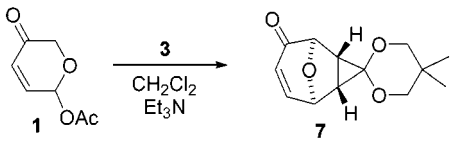
Scheme 2



of **6** is consistent with precedents on the cycloaddition of **3** to carbonyl derivatives,[8] the obtention of **5** is somewhat surprising given that this type of (3+2) annulation seems to require olefins bearing two geminal electron-withdrawing substituents.[6a]

Remarkably, treatment of a CH_2Cl_2 solution of **1** with 1.5 equiv of **3** in the presence of Et_3N (0 °C to room temperature) smoothly provided the *exo* [5C+2C] cycloadduct **7** in a 66% yield. Increasing the amount of the cyclopropene to 2.5 equiv gave an excellent yield of this tricyclic product (91%). The *exo* stereochemistry of the adduct was easily ascertained by the observation in the ^1H NMR spectrum of a negligible coupling constant between the cyclopropyl and the oxa-bridgehead hydrogens. Therefore, although nonactivated olefins fail to participate as dipolarophiles in intermolecular oxidopyrylium ylide cycloadditions,[1] a stable but strained alkene such as **3** is an excellent partner in this reaction.

Scheme 3



Having obtained the adduct **7** we were compelled to demonstrate that the presence of the strained cyclopropyl ring yields interesting possibilities to further manipulate the molecule, with ring expansion to a cyclooctanyl system being among the most attractive. Given that **7** remained unaltered upon prolonged heating in toluene (sealed tube, 160 °C), we tested its behavior upon treatment with reagents previously used to cleave other cyclopropane systems.[9] Attempts to induce a radical cleavage by reaction with Br_2 and light gave a complex mixture of products. Treatment with H_2 in the presence of active Pd or Pt catalyst gave reduction reactions of the enone moiety of the system, while the cyclopropyl ring remained unchanged.

On the other hand, subjecting **7** to acidic conditions (TFA/H_2O, AcOH/THF/H_2O, or Ac_2O/TMSOTf) gave mixtures of several products, which were difficult to analyze. The presence of the enone made the study of the reactivity of the cyclopropane portion of the system somewhat difficult, and so we preferred to continue our assays with the hydroxyl derivative **8a**, which is readily obtained by treatment of **7** with $NaBH_4/CaCl_2$ (93% yield). A quick review of several sets of reaction conditions led us to discover that treatment of a solution of **8a** in Ac_2O with 30 mol % of TMSOTf (0 °C)[10] gave two major products whose spectroscopic analyses were consistent with the cleavage of the internal bond of the cyclopropyl system.

X-ray crystallographic analysis (Figure 1) confirmed the structure of these products as the cyclooctadiene derivatives **9** and **10**, which were isolated in 35% and 34% yields, respectively. Although several methods to cleave 1,1-dialkoxycyclopropanes have been described, most of them lead to fragmentation of the 1,2-carbon−carbon bond,[11]

(5) The cycloaddition of diphenylcyclopropenone to 3-oxido-2,4,6-triphenylpyrylium ylide has been reported: Potts, K. T.; Elliot, A. J.; Sorm, M. *J. Org. Chem.* **1972**, *37*, 3838.

(6) (a) Boger, D. L.; Brotherton, C. E. In *Advances in Cycloaddition*; Curran, D. P., Ed.; JAI Press: Greenwich, CT, 1990; Vol. 2, pp 147−219. (b) Tokuyama, H.; Isaka, H.; Nakamura, E. *J. Am. Chem. Soc.* **1992**, *114*, 5223.

(7) The regio- and stereochemistry of **5** was deduced from the coupling patterns observed in the ^1H NMR spectra, and from NOESY and HMBC experiments.

(8) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6695.

(9) (a) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165−198. (b) Coxon, J. M.; Batiste, M. A. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed; J. Wiley and Sons: London, UK, 1987; Chapter 6.

(10) The mixture Ac_2O/TMSOTf seems to be an excellent way to generate highly reactive acylium cations: Zottola, M.; Venkateswara Rao, B.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1991**, 969.

(11) (a) Moss, R. A.; Guo, W.; Hagedorn, A.; Beveridge, R. *J. Chem. Soc., Chem Commun.* **1982**, *19*, 1102. (b) Saigo, K.; Shimada, S.; Hasimoto, Y.; Hasegawa, M. *Chem. Lett.* **1989**, *7*, 1293. (c) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.

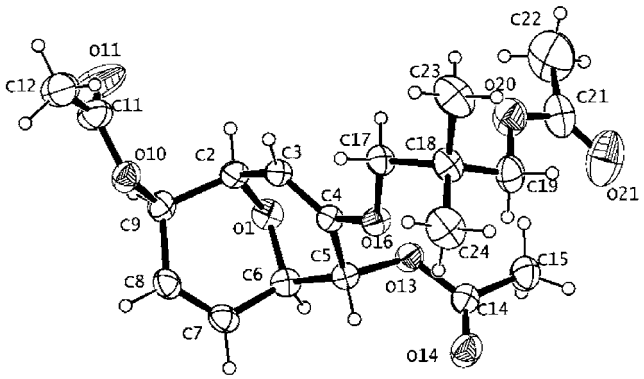
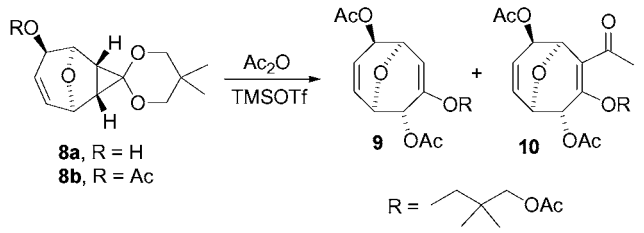


Figure 1. Ortep drawing of the X-ray structure of **9**.[12]

rather than the internal 2,3-bond cleavage observed in this case. Further study of the above ring fragmentation showed

Scheme 4



that the reaction starts with acetylation of the allylic hydroxy group to give **8b**, a reaction that takes place instantaneously even at −78 °C, and that **10** is formed from **9** under the reaction conditions.

As indicated by the results in Table 1, it is possible to control the exclusive formation of **9** by maintaining the

Table 1. Ring Expansion of **8a** to Cyclooctadienes **9** and **10**[a]

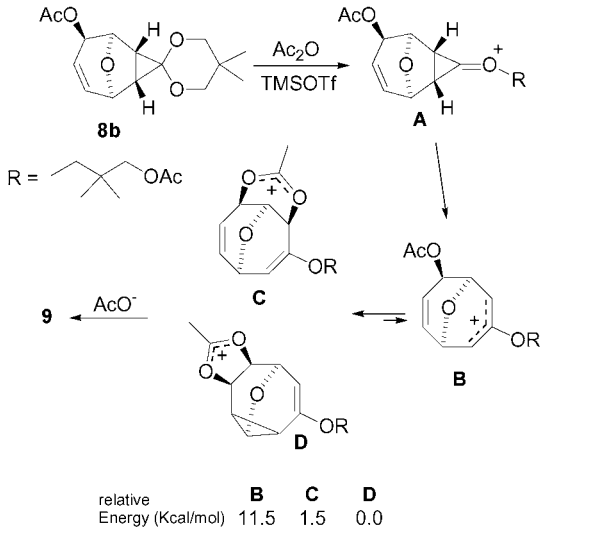
entry	Lewis acid	T^a (°C)	time	ratio **9**/**10**	combined yield (%)
1	TMSOTf	0	4 min	1:1	69
2	TMSOTf	−20	2.5 h	12:1	54 (88)[b]
3	TMSOTf	−40	18 h	1:0	50 (82)
4	TMSOTf[c]	−40	20 h	0:1	35
5	$ZnCl_2$[c]	20	18 h	1:0	47 (58%)

[a] The reactions were carried out with Ac_2O (1 mM) as solvent and 30 mol % of the Lewis acid, unless otherwise indicated. [b] Based on recovered **8b**. [c] Using 1.5 equiv.

reaction temperature at −40 °C (entry 3). Use of higher amounts of TMSOTf led to the immediate formation of mixtures of **8b**, **9**, and **10**, and after several hours of reaction we could only isolate the ketone **10** (entry 4). On the other hand, when the reaction was performed in CH_2Cl_2 in the presence of 10 equiv of Ac_2O, the ring-fragmented products were not formed and the acetylated derivative **8b** was the only product. We have also found that the reactions can be carried out in the presence of $ZnCl_2$ instead of TMSOTf as the activating Lewis acid, although the yields are slightly lower.[13] In this case the reaction requires stoichiometric amounts of $ZnCl_2$ and higher temperatures (entry 5).[14]

The mechanism of the ring-opening reaction most likely involves the initial formation of an oxonium cation **A**, which might then rearrange to a 2-oxoallylcation **B**.[15] Theoretical DFT calculations at the B3LYP-6-31+G* level[16] predict that intermediates **C**, resulting from anchimeric assistance of the neighbor acetate to the allylic cation, or **D**, resulting from an homoallyl−cyclopropylcarbinyl cation rearrangement,[17] are considerably more stable than **B**. Thereby it seems reasonable to surmise that the acetate capture occurs on one of these intermediates, although a definitive conclusion must await further data. The presence of these types of intermediates may therefore be responsible for the observed regio- and stereoselectivity of the process (Figure 2), although the

Scheme 5



inherent face accessibility of the oxabicyclic system could also justify the diastereoselectivity outcome. In summary,

(12) The X-ray structure of **10** is included in the Supporting Information.

(13) With $ZnCl_2$ we have detected small amounts (<10%) of a product similar to **9** but with a chloride instead of an acetate α to the enolether.

(14) Using 30 mol % of $ZnCl_2$, at room temperature, leads exclusively to the acetylated derivative **8b**.

(15) (a) Desai, P.; Aubé, J. *Org. Lett.* **2000**, *2*, 1657. (b) Andes Hess, B., Jr.; Eckart, U.; Fabian, J. *J. Am. Chem. Soc.* **1998**, *120*, 12310.

(16) For the calculations we used the set of programs Gaussian 98: Frisch, M. J.; Trucks, G. W.; Schelegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrewski, V. G.; Montgomery, J. J. A.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennuci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ciolowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; González, C.; Challacombe, M.; Gill, P. M.; Johnson, B.; Chen, W.; Wong, M. W.; Andrés, J. L.; González, C.; Gordon, M. H.; Replogle, E. S.; Pople, J. A. *Gaussian 98*; Gaussian, Inc: Pittsburgh, PA, 1998.

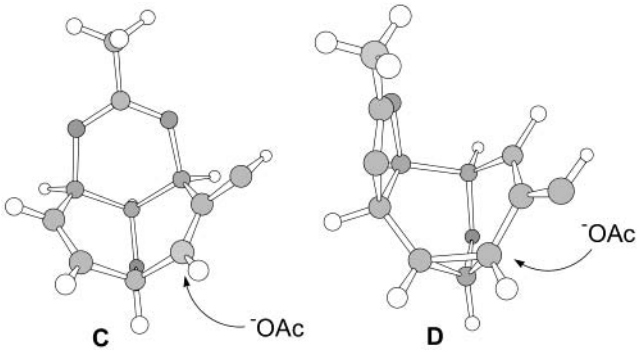


Figure 2. DFT minimized structures of intermediates **C** and **D**, and proposed approach of the nucleophile. Note that for the modeling we have used R = H.

highly functionalized, stereochemically rich 1,5-oxa-bridged cyclooctanes, compounds of potential high synthetic value that are not easy to make with currently available procedures, can be constructed in three simple steps by combining a [5C+2C] oxidopyrylium−cyclopropenone acetal cycloadditon and a subsequent cyclopropanone ring-opening reaction. Overall, the process, which is highly regio- and stereoselective, can be formally considered as a [5C+3C] cycloaddition. Work to unmask the carbocycle in the 9-oxabicyclo[3.3.1]nonadiene products and to further study the scope and generality of both the cycloaddition and the ring-opening method is underway.

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Supporting Information Available: Characterization data and experimental procedures for the preparation of **5**−**10**, and details of the theoretical calculations and the X-ray structure of **10**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Burger, U.; Sonney, J.-M.; Vogel, P. *Tetrahedron Lett.* **1978**, 829. (b) Burger, U.; Sonney, J.-M.; Vogel, P. *Helv. Chim. Acta* **1980**, *63*, 1006.