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Unique Reactivity of *anti*- and *syn*-Acetoxypyranones en Route to Oxidopyrylium Intermediates Leading to a Cascade Process

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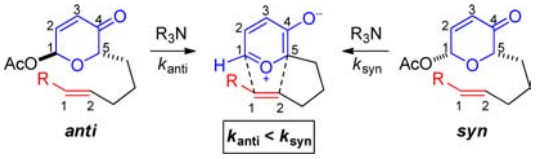
ABSTRACT

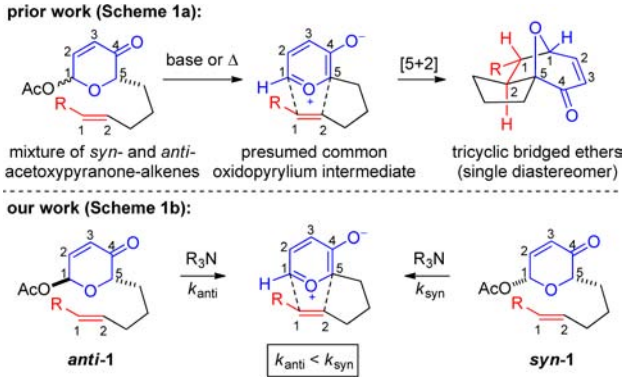


Unique reactivity of *anti*- and *syn*-acetoxypyranones was observed in oxidopyrylium-alkene [5 + 2] cycloadditions. The subtle interplay between the corresponding acetoxypyranone conformation and steric bulk of tertiary amine bases causes *syn*-acetoxypyranones to undergo [5 + 2] cycloaddition appreciably faster than *anti*-acetoxypyranones. Additionally, the efficiency of a cascade process that afforded a novel tetracyclic lactol was determined to be dependent on the relative stereochemistry of each diastereomer, the amine base utilized, and the addition of water.

Cycloadditions constitute an efficient avenue toward the synthesis of seven-membered ring systems.[1] Oxidopyrylium-alkene [5 + 2] cycloadditions give bridged, polycyclic ethers which are common to many biologically active natural products.[2] Although many routes toward oxidopyrylium intermediates have been disclosed, base-mediated or thermal conversion of acetoxypyranones[3] derived from Achmatowicz rearrangement of readily available furfuryl alcohols remains one of the most practical and versatile pathways.[4] Intramolecular variants were first reported by Sammes to deliver bridged, tricyclic ethers (Scheme 1a).[5] More recently, Jacobsen disclosed an elegant approach toward enantioselective, intramolecular [5 + 2] cycloadditions of similar substrates.[6]

Herein, we report the unique reactivity of *anti*- and *syn*-acetoxypyranones **1** toward oxidopyrylium-alkene [5 + 2] cycloadditions (Scheme 1b). Investigation of various amine base-mediated [5 + 2] cycloadditions revealed a general trend of *syn*-**1** reacting faster than *anti*-**1**.

Scheme 1. Acetoxypyranone Conversion to Oxidopyrylium Intermediates toward Intramolecular [5 + 2] Cycloadditions



[†] E.L.W. and J.A.S. contributed equally.

(1) Pellissier, H. *Adv. Synth. Catal.* **2011**, *353*, 189.
(2) Singh, V.; Krishna, U. M.; Vikrant; Trivedi, G. K. *Tetrahedron* **2008**, *64*, 3405.
(3) Hendrickson, J. B.; Farina, J. S. *J. Org. Chem.* **1980**, *45*, 3359.
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(5) Sammes, P. G.; Street, L. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1056.
(6) Burns, N. Z.; Witten, M. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2011**, *133*, 14578.

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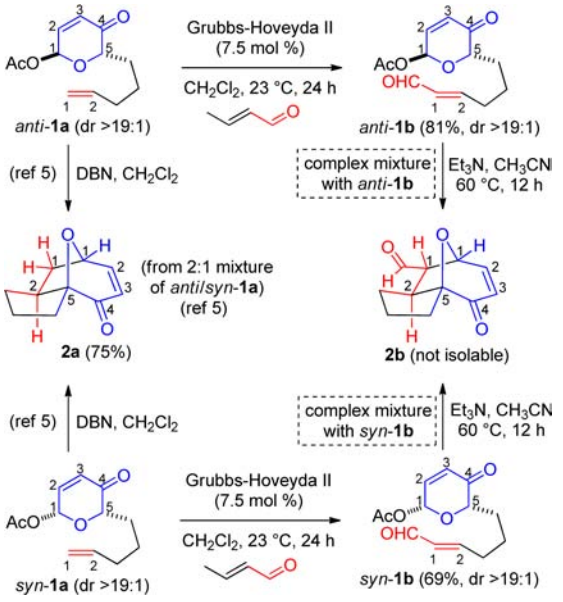
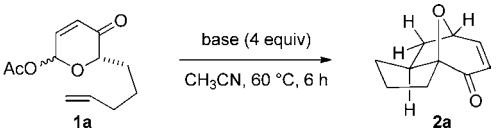
Upon preparation of the known acetoxypyranone **1a** (dr ~2:1) previously utilized directly by Sammes en route to tricylic ether **2a** (75% yield),[5] the mixture was separated via SiO_2 flash column chromatography to deliver diastereomerically pure (> 19:1 as determined by ^1H NMR analysis) acetoxypyranones *anti*- and *syn*-**1a** (Scheme 2). The relative stereochemistry of each diastereomer was confirmed by NOE analysis of *syn*-**1a** and X-ray crytallographic analysis of the corresponding *p*-bromobenzoate analog.[7] For the purposes of this study, the reactivity of each acetoxypyranone diastereomer was evaluated separately. Our initial investigation focused on the attempted intramolecular cycloaddition of *anti*- and *syn*-acetoxypyranone-enals **1b**, which were prepared separately from *anti*- and *syn*-**1a** via Grubbs–Hoveyda cross-metathesis with crotonaldehyde.[8] Although a complex mixture was obtained and tricyclic ether **2b** could not be isolated,[9] we were intrigued by the differing rates and product distributions for each diastereomer. As a result of these initial studies, we chose to investigate the reactivity of each acetoxypyranone diastereomer *anti*- and *syn*-**1a** more thoroughly.

Scheme 2. Attempted Cyclization of Acetoxypyranone-Enals **1b**



Screening of amine bases at 60 °C in acetonitrile revealed varying degrees of conversion with *N*-methylpyrrolidine (NMP), quinuclidine (QUIN), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 1,8-diaza-bicyclo[5.4.0]undec-7-ene (DBU) all providing complete consumption of starting acetoxypyranone (Table 1). From this base screen, three clear trends emerged. First, from the pairwise comparison of structurally similar bases such as *N*-methylmorpholine and *N*-methylpiperidine (entries 4,7), it is apparent that the electronic effects of sterically comparable bases play an important role. Second, the decreased steric hindrance of bases with similar pK_a values also plays a significant role, which is best illustrated by the increasing conversion trend observed from *N*,*N*-diisopropylethyl amine, triethylamine, *N*-methylpiperidine, NMP, and QUIN (entries 5–9). Lastly, these results demonstrate that *syn*-acetoxypyranone **1a** consistently undergoes conversion to tricyclic ether **2a** at a qualitatively faster rate than *anti*-acetoxypyranone **1a**.

Table 1. Initial Screening of Amine Bases



entry	base	*anti*-**1a**/**2a** (% yield)[a]	*syn*-**1a**/**2a** (% yield)[a]
1	none	99/0	93/0
2	pyridine	88/0	90/2
4	*N*-methylmorpholine	89/5	68/14
5	*N*,*N*-diisopropylethyl amine	86/5	68/14
6	triethylamine	62/36	6/80
7	*N*-methylpiperidine	59/41	7/89
8	*N*-methylpyrrolidine	0/88	0/91
9	quinuclidine	0/90	0/95
10	1,4-diazabicyclo[2.2.2]octane	0/81	0/88
11	1,8-diazabicyclo[5.4.0]undec-7-ene	0/34	0/37

[a] Determined by ^1H NMR analysis utilizing 1,3,5-trimethoxybenzene as the internal standard.

To probe the base dependency, four effective bases (NMP, DABCO, QUIN, and DBU) were subjected to various solvents at ambient temperature (Table 2). It was determined that QUIN and DBU are the most efficient bases and that CH_2Cl_2 and CH_3CN are the most efficient solvents (entries 11,12 and 15,16). With these conditions, both the steric and electronic phenomena were further validated since QUIN is less hindered than NMP and DABCO is inductively deactivated compared to QUIN. Perhaps indicative of the unique reactivity patterns of DBU,[10] utilizing a single equivalent led to the increased yield of ether **2a** (i.e., Table 1, entry 11 vs Table 2, entry 16). Excess DBU and use of other bases such as imidazole afforded complex mixtures of unidentified products.

In order to confirm the generality of this qualitative rate difference, the same bases were tested in CH_3CN with an electron-donating alkene (**1c**) and an electron-withdrawing alkene (**1d**) (Table 3).[7] Although some variation was exhibited, these conversion results further validate the general rate enhancement for the *syn*-acetoxypyranones **1c,d** toward cycloadducts **2c,d** and the aforementioned steric and electronic trends (*vide supra*).[6]

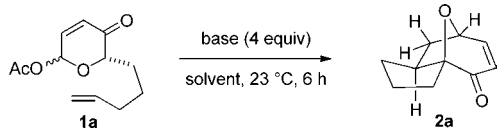
(7) See Supporting Information for further details.

(8) (a) Movassaghi, M.; Tjandra, M.; Qi, J. *J. Am. Chem. Soc.* **2009**, *131*, 9648. (b) Chatterjee, A.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (c) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *624*, 327. (d) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

(9) ^1H NMR analysis of the crude reaction mixtures indicated a trace quantity of aldehyde **2b** with multiple byproducts.

(10) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311.

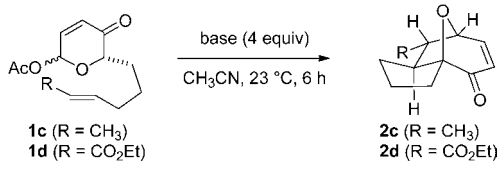
Table 2. Solvent Screening of Selected Amine Bases



entry	solvent	base	*anti*-**1a**/**2a** (% yield)[a]	*syn*-**1a**/**2a** (% yield)[a]
1	THF	NMP[b]	92/3	68/6
2	THF	DABCO[c]	91/8	69/12
3	THF	QUIN[d]	44/22	42/32
4	THF	DBU[e]	7/68	5/80
5	tol.	NMP[b]	71/2	44/5
6	tol.	DABCO[c]	69/6	28/7
7	tol.	QUIN[d]	58/18	39/32
8	tol.	DBU[e]	5/48	0/27
9	DCM	NMP[b]	79/13	35/26
10	DCM	DABCO[c]	86/18	62/23
11	DCM	QUIN[d]	30/39	14/63
12	DCM	DBU[e]	3/68	0/77
13	CH_3CN	NMP[b]	68/25	38/42
14	CH_3CN	DABCO[c]	48/39	31/61
15	CH_3CN	QUIN[d]	0/69	0/83
16	CH_3CN	DBU[e]	0/78	0/58

[a] Determined by ^1H NMR analysis utilizing 1,3,5-trimethoxybenzene as the internal standard. [b] *N*-Methylpyrrolidine. [c] 1,4-Diazabicyclo[2.2.2]-octane. [d] Quinuclidine. [e] 1,8-Diazabicyclo[5.4.0]undec-7-ene (only 1 equiv was utilized).

Table 3. Conversion of Substituted Acetoxypyranones **1c**–**d**

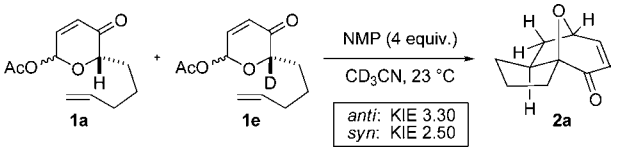


entry	R (**a**/**b**)	base	*anti*-**1/2** (% yield)[a]	*syn*-**1/2** (% yield)[a]
1	CH_3 (**c**)	NMP[b]	60/16	20/48
2	CH_3 (**c**)	DABCO[c]	43/33	27/43
3	CH_3 (**c**)	QUIN[d]	2/47	0/47
4	CH_3 (**c**)	DBU[e]	0/18	0/14
5	CO_2Et (**d**)	NMP[b]	42/39	12/69
6	CO_2Et (**d**)	DABCO[c]	28/51	12/72
7	CO_2Et (**d**)	QUIN[d]	0/76	0/87
8	CO_2Et (**d**)	DBU[e]	0/68	0/70

[a] Determined by ^1H NMR analysis utilizing 1,3,5-trimethoxybenzene as the internal standard. [b] *N*-Methylpyrrolidine. [c] 1,4-Diazabicyclo-[2.2.2]octane. [d] Quinuclidine. [e] 1,8-Diazabicyclo[5.4.0]undec-7-ene (only 1 equiv was utilized).

We proposed that deprotonation was involved in the rate-determing step, and thus studies were undertaken that revealed primary kinetic isotope effects (KIE) for both ^2H-labeled acetoxypyranones *anti*-**1e** and *syn*-**1e** (Scheme 3).[11] This provided evidence that abstraction of H(D) is involved in the rate-determining step suggestive of early transition states[12] that resemble low energy conformations of *anti*-**1a** and *syn*-**1a**, respectively (*vide infra*).

Scheme 3. KIE Studies of ^2H-Labeled Acetoxypyranones **1e**



From the calculated[7,13] ground-state conformation of *anti*-**1a** (Figure 1), it was observed that the acetate group adopts an anomeric configuration (pseudoaxial) which puts the α-proton in an ideal orientation for extraction. In the case of *syn*-**1a**, the calculated ground state conformation (not shown)[7] also reveals an anomeric acetate resulting in a presumably unproductive pseudoequatorial orientation of the α-proton. Curtin–Hammitt/Winstein–Holness kinetic principles[14] likely are operative, as a conformational ring flip of *syn*-**1a** (< 1 kcal higher in energy) would induce the α-proton to reside in the pseudoaxial position which is perpendicular to the adjacent ketone and thus serve as the reactive species (Figure 1). Whereas the acetate group of *anti*-**1a** is pseudoaxial resulting in greater steric hindrance around the acidic proton, the acetate of the proposed reactive conformation of *syn*-**1a** is pseudoequatorial and projects away from the acidic proton. The steric hindrance present in the ground-state conformation of *anti*-**1a** sheds light on corresponding steric interactions in the proposed early transition state which lead to slower reactivity.

Based on these data, a proposed reaction pathway can be envisioned (Scheme 4). Both *anti*- and *syn*-**I** likely adopt conformations in which the α-proton is coplanar with the π-system of the ketone. Rate-determining deprotonation delivers dienolates **III** and *ent*-**III** that likely have very short lifetimes due to the impending aromaticity. The enantiomeric relationship between these dienolates **III** and *ent*-**III** gives further creedance to the proposed rate-determining deprotonation since they would rapidly coalesce, thus essentially destroying the inherent difference and bias between acetoxypyranone diastereomers *anti*- and *syn*-**I**. However, it is also important to consider the possibility of slightly different reaction pathways. For example, it is conceivable that formation of oxidopyrylium **IV** via *anti*-**I**, although slower, is more concerted due to the anomeric orientation of the acetate moiety. In either case, elimination of the acetoxy would deliver the oxidopyrylium **IV**, which undergoes *endo* [5 + 2] cycloaddition (*i.e.*, *endo*-**V**).[2,6]

(11) Melander, L.; Saunders, W. H., Jr. *Reaction Rates of Isotopic Molecules*; Wiley and Sons: New York, 1980.

(12) Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.

(13) Conformational analysis (Spartan '02, Wavefunction, Inc.) using MMFF94 force field, optimization (Gaussian '03), and B3LYP, 6-31g**, Gaussian, Inc.: Wallingford CT, 2004.

(14) (a) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83–134. (b) Seeman, J. I. *J. Chem. Educ.* 1986, *63*, 42.

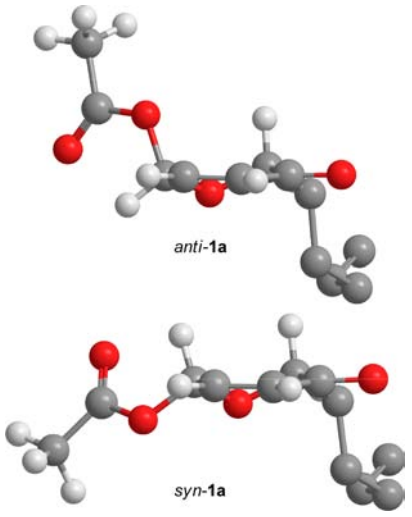
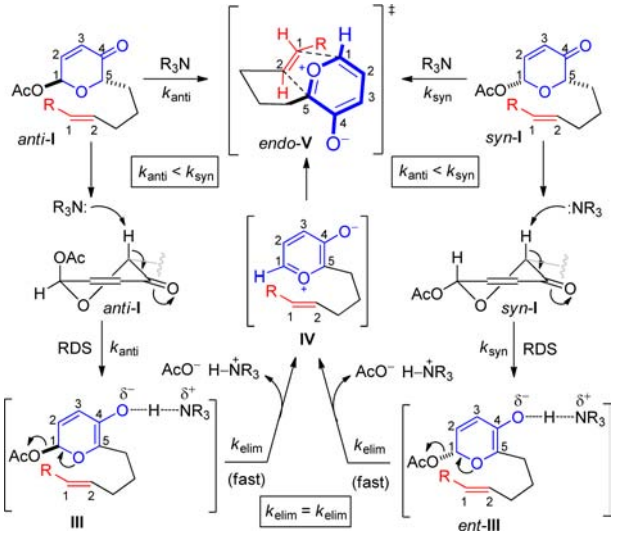


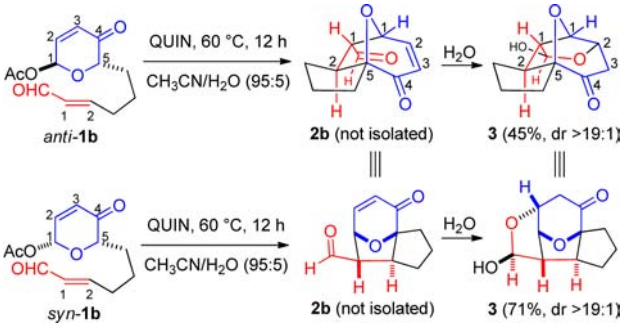
Figure 1. Representations of proposed reactive conformers *anti*- and *syn*-**1a** with pseudoaxial hydrogens perpendicular to the ketone (hydrogens removed from tether for clarity).

Scheme 4. Proposed Pathway toward Oxidopyrylium **IV**



In the process of investigating reactivity differences of acetoxypyranone diastereomers, it was previously observed that acetoxypyranone-enals *anti*- and *syn*-**1b** were unproductive (*cf.*, Scheme 2), which is attributed to further reaction of the presumed cycloadduct **2b** with adventitious water (Scheme 5).[15] Continued investigation of acetoxypyranone-enals *anti*- and *syn*-**1b** based upon the optimized quinuclidine conditions in CH_3CN/H_2O delivered lactol **3**

Scheme 5. Cascade Process toward Lactol **3**



in reasonable yields. Although [5 + 2] cycloaddition is believed to occur first, the corresponding bridged, tricyclic ether **2b** is not isolable. Water presumably attacks the aldehyde in concert with the conjugate addition[16] in a facile process delivering the novel caged lactol **3**. It is noteworthy that increased efficiency was observed with quinuclidine as compared to alternative amine bases, especially in the case of acetoxypyranone *anti*-**1b**. DBU, for example, afforded complex mixtures of lactol **3** even with 1 equiv. The diminished efficiency toward lactol **3** with acetoxypyranone *anti*-**1b** is attributed to additional byproducts not observed with *syn*-**1b** that have proven difficult to isolate and characterize, but are still under investigation. In any event, this unique oxidopyrylium-alkene [5 + 2] cycloaddition conjugate addition cascade sequence[17] constructs 3 bonds, 3 rings, and 5 stereocenters to afford a novel tetracyclic lactol **3** from readily accessible acetoxypyranone-enals **1b**.

The unique reactivity of *anti*- and *syn*-acetoxypyranone diastereomers was demonstrated in oxidopyrylium-alkene [5 + 2] cycloadditions. Due to the subtle interplay between acetoxypyranone conformations and steric bulk of tertiary amine bases, *syn*-acetoxypyranones consistently undergo cycloaddition faster than the corresponding *anti*-acetoxypyranones. Additionally, the efficiency of an oxidopyrylium-alkene [5 + 2] cycloaddition conjugate addition cascade process that afforded a novel tetracyclic lactol was determined to be dependent upon the relative stereochemistry of the acetoxypyranone, the amine base utilized, and the addition of water. Further studies directed at a deeper understanding of this process and synthetic applications will be reported in due course.

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Supporting Information Available. Full experimental data. This material is available free of charge via the Internet http://pubs.acs.org.

The authors declare no competing financial interest.

(15) Trace lactol **3** was observed without intentional addition of H_2O.

(16) For a similar, stepwise conjugate addition, see: Snider, B. B.; Wu, X.; Nakamura, S.; Hashimoto, S. *Org. Lett.* **2007**, *9*, 873.

(17) (a) Enders, D.; Grondal, C.; Huttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570. (b) Nicolaou, K. C.; Montagnon, T.; Snyder, S. A. *Chem. Commun.* **2003**, 551. (c) Tietze, L. *Chem. Rev.* **1996**, *96*, 115.