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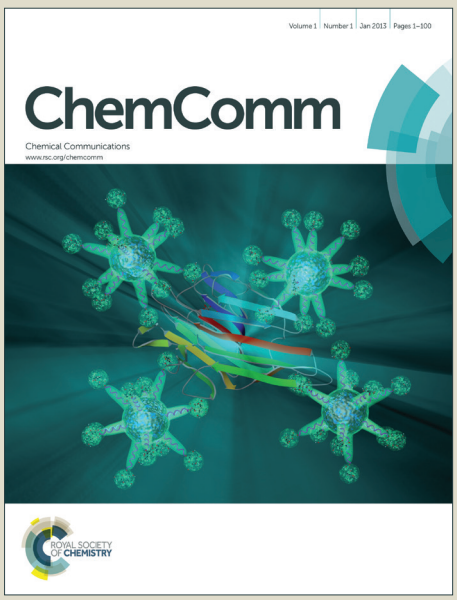

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Investigation of Oxidopyrylium-Alkene [5 + 2] Cycloaddition Conjugate Addition Cascade (C^3) Sequences

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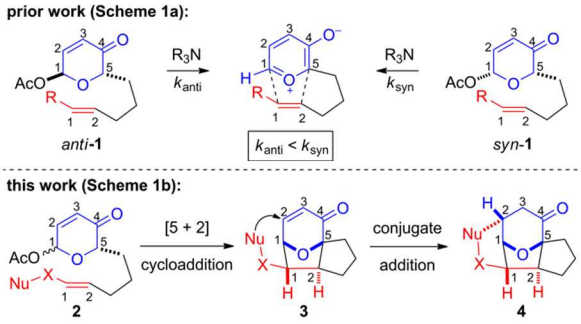
Novel oxidopyrylium-alkene [5 + 2] cycloaddition conjugate addition cascade (C^3) sequences are described. Various acetoxypyranone-alkenes with pendant nucleophiles undergo [5 + 2] cycloaddition followed by conjugate addition from the concave face of the intermediate pyranone toward bridged, tetracyclic ethers. In several cases, 3 new rings, 4 new bonds, and 6 new contiguous stereocenters are constructed with excellent diastereoselectivity. Finally, an asynchronous concerted reaction pathway is proposed to explain the high diastereoselectivity of the oxidopyrylium-alkene [5 + 2] C^3.

Cascade sequences, also known as domino, tandem, or multi-component reactions, provide an effective and rapid complexity-building process toward many ring systems.[1] Cycloadditions allow for transformation of flat structures into chiral, three-dimensional moieties[2] representing a critical mode to access seven-membered rings within this context.[3] Specifically, oxidopyrylium-alkene [5 + 2] cycloadditions readily afford bridged, polycyclic ethers[4] similar to those found in biologically active natural products.[5] In our previous report,[6] we observed differing reactivity of *anti*- and *syn*-acetoxypyranones **1** toward presumed oxidopyrylium-alkene intermediates en route to [5 + 2] cycloadditions (Scheme 1a).[7]

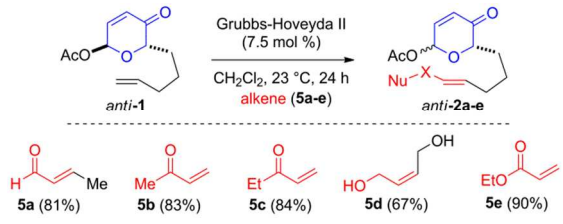
Herein, we report the synthesis of several novel caged ring systems **4** obtained via oxidopyrylium-alkene [5 + 2] cycloaddition conjugate addition cascade (C^3) sequences derived from acetoxypyranone-alkenes **2** with pendant nucleophiles (Scheme 1b).[8] In addition, we report several examples involving conjugate additions of isolable [5 + 2] cycloadducts **3** which revealed key mechanistic information.[9] In several C^3 reaction sequences, as many as 3 new rings, 4 new bonds, and 6 new contiguous stereocenters were constructed as a single diastereomer from readily available starting materials in a single reaction mixture.

Despite attempts to isolate aldehyde **3a**, acetoxypyranone-enal **2a** delivered lactol **4a** (Scheme 3).[6] The spontaneous nature of the concave conjugate addition led us to further probe these reaction sequences. Investigation of stepwise variants revealed fundamental information toward the development of the oxidopyrylium-alkene [5 + 2] C^3. In contrast to pyranone-aldehyde **3a**, consistent isolation of pyranone-ketones **3b,c** was achievable which provided key mechanistic information regarding the proposed reaction pathway (*vide infra*). Pyranone-ketones **3b,c** were subsequently converted to lactols **4b,c** under basic conditions with aq. LiOH (eq. 2-3). In addition, [5 + 2] cycloaddition with allylic alcohol **2d** (*E:Z* 7.4:1)[11] at ambient temperature afforded cycloadduct **4d** in 51% yield with only trace pyranone-alcohol **3d** observed by crude ^{1}H NMR analysis (eq. 4). Pyranone-ethyl ester **3e**, derived from acetoxypyranone-ethyl ester **2e**, was converted to the tetracyclic lactol **4e** via a stepwise sequence consisting of LiOH-mediated hydrolysis followed by μW-assisted[12] conjugate addition (eq. 5). Lastly, [5 + 2] cycloaddition of silyl ether *anti*-**2f** (*E:Z* 10:1)[11] afforded cycloadduct **3f** and was converted to bis-ether **4d** through a TBAF-mediated silyl deprotection-conjugate addition (eq. 6).

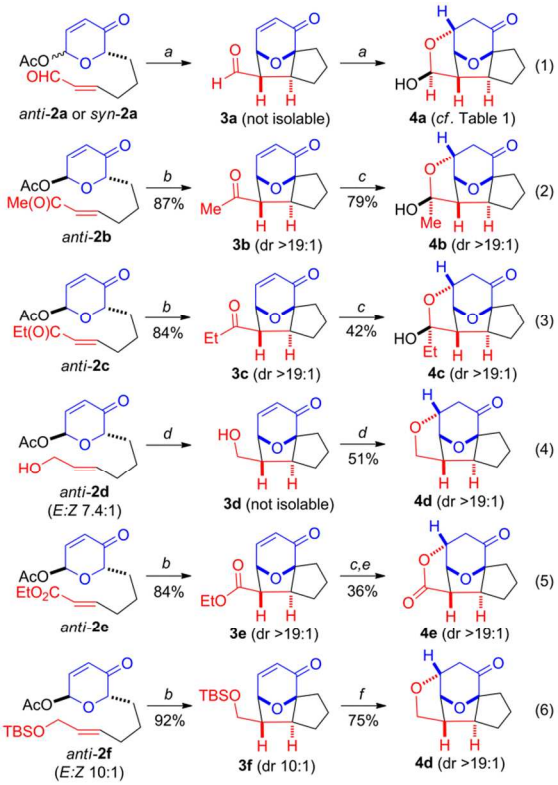
Scheme 1. Intramolecular Oxidopyrylium-Alkene [5 + 2] Cycloaddition Conjugate Addition Cascade (C^3)



Scheme 2. Cross-Metathesis to *anti*-Acetoxypyranones 2a-e



Scheme 3. Investigation of a Stepwise Oxidopyrylium-Alkene [5 + 2] Conjugate Addition Sequence

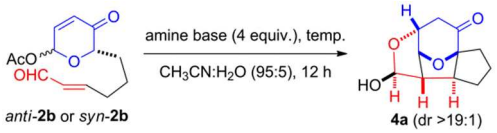


[a] See Table 1. [b] *N*-methylpyrrolidine, CH_3CN, 60 °C. [c] aq. LiOH, 23 °C. [d] DABCO, CH_3CN, 23 °C. [e] CH_3CN, μW (120 °C), 20 min. [f] TBAF, THF, 0→23 °C.

Consistent with our previous findings regarding the different rates of cycloaddition for *anti*- and *syn*-acetoxypyranone-alkenes **1**, we observed significantly increased efficiency of *syn*-acetoxypyranone **2a** (71%) compared to *anti*-acetoxypyranone **2a** (45%) toward lactol **4a** (Table 1, entries 1-2).[6] In order to determine if tedious separation of diastereomers was necessary, acetoxypyranone **2a** as a mixture (*anti*:*syn* 3.5:1) was subjected to identical conditions which afforded a satisfactory 55% yield of lactol **4a** (entry 3). DBU and triethylamine, the most common bases utilized in oxidopyrylium-alkene [5 + 2] cycloadditions,[4,5] were much less efficient for this cascade process (entries 4-5). Thus far, utilization of *N*-methylpyrrolidine and DABCO has proven to be the most efficient and cost effective strategy (entries 6-7). Consequently, reduced reaction temperatures were tolerated resulting in slightly increased yield (entry 8).

Compared to the facile conversion of pyranone-aldehyde **2a** to afford lactol **4a** (*cf.* Table 1), conjugate addition of the pyranone-ketone **3b** derived from acetoxypyranone-enone **2b** was non-spontaneous (Table 2). Whereas lactol **4a** was observed even without addition of water,[13] lactol **4b** was not detected under similar conditions (*cf.* Scheme 3, eq. 2). Interestingly, upon addition of water (5%), trace lactol **4b** was observed (entry 1) which was confirmed by the synthesis of the same lactol **4b** in the stepwise approach (*cf.* Scheme 3, eq. 2). Simply increasing the concentration of water proved to be sufficient to afford the desired lactol **4b**, which was isolated in 75% yield with only minor quantity of enone-ketone **3b** (entry 2). Similarly, acetoxypyranone-enone **2c** afforded the analogous lactol **4c** albeit with slightly decreased conversion of the intermediate pyranone-enone **3c** (entry 3).

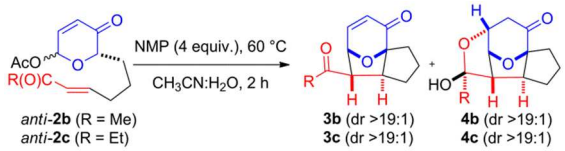
Table 1. Acetoxypyranone-Enal 2a [5 + 2] C[3]



entry	*anti*/*syn* (dr)[a]	amine base	temp. (°C)	**4a** (% yield)[b]
1	1:>19	QUIN[c]	60	71
2	>19:1	QUIN[c]	60	45
3	3.5:1	QUIN[c]	60	55
4	3.5:1	DBU[d]	60	ND[h]
5	3.5:1	TEA[e]	60	<30[i]
6	3.5:1	NMP[f]	60	63
7	3.5:1	DABCO[g]	60	63
8	3.5:1	DABCO[g]	23	69

[a] Determined by ^{1}H NMR analysis of chromatographically purified **2b**. [b] Isolated yield. [c] quinuclidine. [d] 1,8-diazabicyclo[5.4.0]undec-7-ene (only one equiv. was utilized). [e] triethylamine. [f] *N*-methylpyrrolidine. [g] 1,4-diazabicyclo[2.2.2]-octane. [h] Not detected; complex mixture was observed. [i] Isolated yield, but inseparable impurities remained.

Table 2. Acetoxypyranone-Enone 2b,c [5 + 2] C[3]

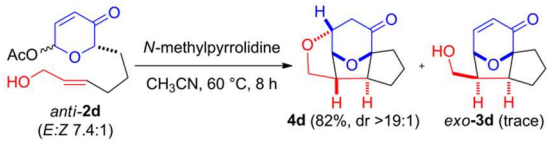


entry	enone	CH_3CN/H_2O	**3b/3c** (% yield)[a]	**4b/4c** (% yield)[a]
1	**2b**	95:5	80	<5[b]
2	**2b**	50:50	6	75
3	**2c**	50:50	16	64

[a] Isolated yield. [b] Trace quantity was detected by ^{1}H NMR analysis of the crude reaction mixture.

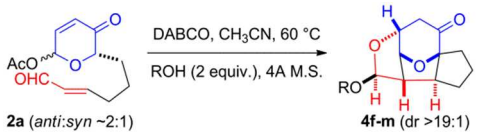
Whereas cross-metathesis provided α,β–unsaturated carbonyls (*i.e.* **2a-c,e**) with excellent *E*-selectivity, cross-metathesis with **5d** afforded moderate *E*-selectivity (7.4:1) of the desired *anti*-**2d** (*cf.* Scheme 3, eq. 4).[10] This mixture of acetoxypyranone-alcohol **2d** was treated with DBU (not shown), but gave poor yield of bis-ether **4d**. As discussed previously (*cf.* Scheme 3, eq. 4), treatment with DABCO at room temperature for 24 hours delivered the desired bis-ether **4d** in considerably better yield with only trace quantity of **3d** observed. Heating with *N*-methylpyrrolidine for 8 hours provided good yield of bis-ether **4d** (Scheme 4). Unable to undergo conjugate addition from the convex face, pyranone-alcohol *exo*-**3d** arising from [5 + 2] cycloaddition of the minor *Z*-allylic alcohol **2d** was also isolated and characterized.[11]

Scheme 4. Acetoxypyranone-Allylic Alcohol 2d [5 + 2] C^3



In an effort to extend the scope of this oxidopyrylium-alkene [5 + 2] cycloaddition conjugate addition cascade (C^3), we treated acetoxypyranone-enal **2a** with a variety of alcohols (as opposed to water) to provide highly functionalized, caged acetal-ethers **4f-m** (Table 3). Utilization of excess methanol (CH_3CN:MeOH 95:5) with 3Å molecular sieves to ensure the exclusion of water provided acetal **4f** as a single diastereomer in 63% yield (entry 1). Additional functionalized primary alcohols afforded similar results (entries 2-4). More hindered alcohols gave mixed results; isopropanol delivered acetal **4j** in moderate yield (entry 5), but *tert*-amyl alcohol afforded a complex mixture with no acetal **4k** detected (entry 6). Although *p*-cresol gave poor yield, acetal **4l** represents an interesting result arising from a very different hydroxyl functionality (*i.e.* phenol) attacking the presumed pyranone-aldehyde **3a** (entry 7). Finally, highly functionalized Boc-L-serine methyl ester provided acetal **4m** in good yield as an expected mixture of inseparable diastereomers (entry 8).

Table 3. Acetoxypyranone-Enal 2a [5 + 2] C^3 with Alcohols

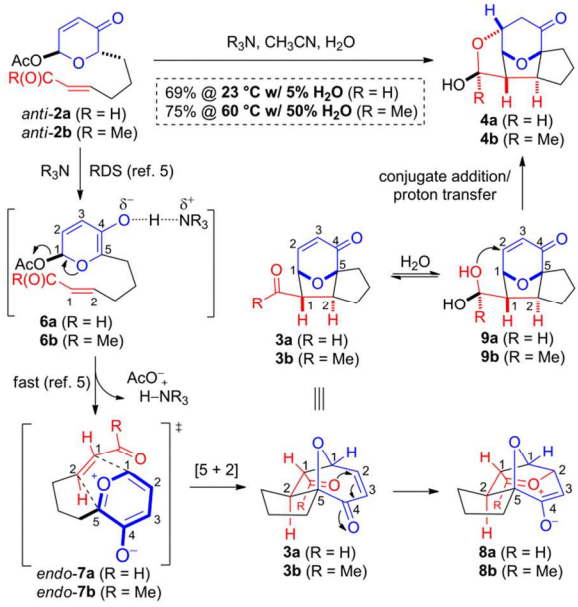


entry	ROH	time (h)	**4f-m** (% yield)[a]
1	MeOH[b]	6	63 (**f**)
2	H_2C=$CH(CH_2)_4OH$	6	53 (**g**)
3	*p*-$MeO(C_6H_4)CH_2OH$	1	62 (**h**)
4	HC≡CCH_2OH	2.5	57 (**i**)
5	*i*-PrOH	4	53 (**j**)
6	2-methyl-2-butanol	6	ND (**k**)[c]
7	*p*-$Me(C_6H_4)OH$	2.5	20 (**l**)
8	Boc-L-serine methyl ester	1	73 (**m**)[d]

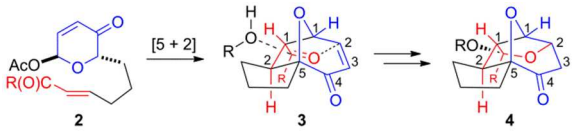
[a] Isolated yield. [b] 5% MeOH and 3Å M.S. were utilized. [c] Not detected. [d] Isolated as a 1:1 mixture of amino acid diastereomers.

A reaction pathway comparing acetoxypyranone-enal **2a** and acetoxypyranone-enone **2b** is proposed (Schemes 5-6). Based upon our previous findings,[6] we suggest that rate-determining deprotonation followed by expulsion of the acetate affords oxidopyrylium-alkene **7a** or **7b**. Upon *endo*-selective [5 + 2] cycloaddition, either pyranone-aldehyde **3a** or pyranone-ketone **3b** would be produced. Upon initial consideration, there seemed to be two plausible mechanistic scenarios: conjugate addition from the concave face may be advanced via oxocarbenium **8** or hydrate **9** (Scheme 5). Whereas formation of hydrate **9a** from aldehyde **3a** followed by spontaneous conjugate addition would afford lactol **4a**, the corresponding ketone **3b** would be far less prone to initial hydrate **9b** formation and therefore require increased reaction temperature and greater concentration of water. Although this mechanism involving initial formation of hydrate **9** seems plausible, it does little to explain the observed high diastereoselectivity as confirmed by x-ray crystallographic analysis in multiple cases.[11] In contrast, a mechanism involving formation of oxocarbenium **8** would provide a satisfying rationalization of diastereoselectivity via attack of the nucleophile from the convex face, but it does not explain the more facile reaction of aldehyde **3a** as compared to ketone **3b**.[14] A third scenario, however, is an asynchronous concerted pathway in which neither hydrate **9** nor oxocarbenium **8** are discrete intermediates, but rather both O–C bonds are generated simultaneously (Scheme 6). Based upon conformational analysis and ground state energy calculations,[11] selective formation of a single diastereomer of lactol **4a** seems unlikely assuming free rotation of hydrate **9a**. Similar analysis of corresponding hemiacetals derived from alcohols (not shown) suggests that significant quantities of *epi*-acetals **4f-m** (*cf.* Table 3) would be expected due to the apparent lack of steric facial bias of aldehyde **3a**. Analogous computational studies on methyl ketone **3b** and the corresponding hydrate **9b** suggest that a highly-ordered, asynchronous concerted pathway is plausible. Ground state calculations on ketone **3b** revealed a low energy conformer wherein the lone pair electrons of the ketone are projected toward the π* of the α–β unsaturated carbonyl.[15] This proposed n-π* stabilizing effect clearly leaves one face of the ketone more accessible to nucleophilic attack. Thus, as the nucleophile approaches the carbonyl (ketone **3b** or aldehyde **3a**), spontaneous O–C bond formation would occur via the n-π* coordination in an asynchronous concerted pathway. This is further supported by the observation that methyl ketone **3b** and ethyl ketone **3c** provide the same relative stereochemical outcome of lactols **4b,c** (*cf.* Table 2). More specifically, if free rotation of hydrates **9b,c** prior to conjugate addition was possible, conformational analysis studies suggest that ketone **3c** could preferentially deliver *epi*-lactol **4c** due to increased steric hindrance of the ethyl substituent within the highly congested concave face.

Scheme 5. Potential Reaction Pathways of Oxidopyrylium-Alkene [5 + 2] Cycloaddition Conjugate Addition Cascades



Scheme 6. Proposed Asynchronous Concerted Nucleophilic Attack and Conjugate Addition en Route to the [5 + 2] C^3



Conclusions

Novel oxidopyrylium-alkene [5 + 2] cycloaddition conjugate addition cascade (C^3) reactions have been reported. Readily accessible acetoxypyranone-alkenes with pendant nucleophiles underwent [5 + 2] cycloaddition followed by intramolecular conjugate addition from the concave face of the intermediate pyranones. Several examples were shown in which as many as 3 new rings, 4 new bonds, and 6 new contiguous stereocenters were constructed as a single diastereomer in a single reaction mixture. In order to explain the high diastereoselectivity observed, an asynchronous concerted reaction pathway was proposed. Further investigation of these [5 + 2] C^3 processes toward mechanistic understanding, scope and limitation, and synthetic applications will be reported in due course.

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Notes and references

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†Electronic Supplementary Information (ESI) available: Detailed synthetic information and spectroscopic characterization of all new compounds. See DOI: 10.1039/c000000x/

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