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Citric acid mediated catalytic osmylation/oxidative cleavage of electron deficient olefins: a vinyl sulfone study

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ABSTRACT

The first broad catalytic dihydroxylation of enantiopure cyclic vinyl sulfones followed by oxidative cleavage of the resulting acyloin provides linear termini-differentiated polyketide fragments. This mild vinyl sulfone cleavage provides an effective alternative to the current ozonolysis protocol.

Introduction

Efforts toward optimization of vinyl sulfone polyketide methods for the synthesis of natural products illustrate the effectiveness of five-, six-, and seven-membered cyclic vinyl sulfones to assemble contiguous chiral centers.[1] The vinyl sulfone polypropionate methodology has been utilized to provide cyclic vinyl sulfones for use as termini differentiated polyketide precursors primarily via ozonolysis.[2]

Ozonolysis of electron-rich olefins is widely used and fully documented, as electron-rich olefins are an estimated 10,000 times more reactive to ozone than electron-deficient olefins.[3] Oxidative cleavage of electronically deactivated and/or sterically hindered olefins has proven historically quite difficult. Griesbaum[4] and Fuchs[5] reported the first ozonolysis of vinyl triflates, vinyl nitriles, and vinyl sulfones,[1,2] respectively, in the 1990s. Ozonolysis of seven-membered vinyl sulfones was more extensively studied for the synthesis of polypropionate fragments of apoptolidin and aplyronine A.[6–8]

While ozonolysis of vinyl sulfones has been established as an effective method, it has limitations in the construction of polyketide fragments. Many frequently used protecting groups are incompatible with ozolytic cleavage conditions. Methoxymethyl (MOM) ether used in the total synthesis of lepranthin by Miyashita,[9] methylthiomethyl (MTM) ether employed in the assembly of aplyronine A by Yamada,[10] 2-methoxyethoxymethyl (MEM) ether utilized in anti-fungal soraphen $A_{1\alpha}$ analogs[11] and 1-ethoxyethyl ether included in an examination of the C16–C22 part of irumamycin[12] all react in the presence of ozone.[13] Ozonolysis has also been responsible for unwanted oxidation of secondary alcohols on select cyclic vinyl sulfones to ketones.[14]

The aforementioned considerations demand alternative experimental methods for oxidative cleavage. Mild, more versatile methods would be highly desirable.

Results and discussion

Osmium tetroxide addition to electron-deficient alkenes is typically slow because of diminished reactivity.

Phenyl vinyl sulfones bear a tetrahedral sulfone moiety which is highly sterically shielded (A value >2.5)[15] in addition to being electronically deficient. These features are clearly apparent in the regio- and enantiospecific Jacobsen epoxidation of the terminal olefin of 6- and 7-membered 1,3-dienyl phenyl sulfones (>99% de and ee), leading to the genesis of our polypropionate method.[16–18] Earlier strategies for dealing with the oxidative inertness of vinyl sulfones originally involved reductive cleavage of the sulfone moiety via treatment with BuMgCl/Pd(II)OTf,[19] or Na amalgam.[20] The resulting electron-neutral olefin can then be readily cleaved, but the transformation sacrifices the inherent olefin dissymmetry.

Previous reports on osmium catalyzed dihydroxylation of vinyl sulfones are scarce and highly substrate dependant. Backvall[21] and Fuchs[22] reported osmium catalyzed dihydroxylation of

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torsionally-activated vinyl sulfones α to bridged tetrahydrofurans in yields of 57% for a system with no substituents and 90% with two substituents in the syn position to the oxo bridgehead. In addition Fuchs reported a 90% yield on a cyclic vinyl sulfone with all three substituents occupying the same face of the molecule.

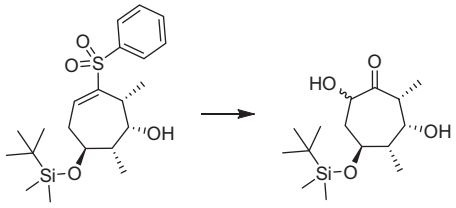
Citric acid has been shown to improve the rates and the yields of *cis*-dihydroxylations of various electron-deficient alkenes (Scheme 1).[23] In addition to acting as a pH buffer by retarding formation of insoluble Os(VIII) dioxoosmate **iii**, citric acid strongly binds to OsO_4 to form **i**. Studies on the effects of citric acid buffered osmium catalyzed dihydroxylation on cyclic vinyl sulfones are herein examined.

Addition of citric acid to improve the catalytic osmylation system led to a greater understanding of the dihydroxylation mechanism as it applies to vinyl sulfone substrates (Scheme 1). As previously mentioned, addition of citric acid to osmium tetroxide gives rise to monoglycolate (**i**). Red-Ox addition of monoglycolate to the vinyl sulfone substrate provides mixed (bis)glycolate (**ii**) Os(VI) species. Rate-limiting hydrolysis of the mixed (bis)glycolate **ii** affords the desired acyloin and Os(VI) monoglycolate **iv**. When the osmylation is performed under homogeneous conditions the co-oxidant *N*-methylmorpholine *N*-oxide (NMO) and base *N*-methylmorpholine (NMM) have access to all intermediates in the catalytic cycle. Alternatively (bis)glycolate **ii·H$_2$O** can be deprotonated by NMM equilibrating to dioxoosmate **iii** thereby causing cessation of the catalytic cycle.

Addition of citric acid assists catalyst turnover by preventing formation of the catalytically unreactive dioxoosmate dianion species **iii**, which is formed upon deprotonation of hydrated (bis)glycolate **ii·H$_2$O** at higher pH. The strong electron withdrawing ability of the sulfone contributes to the acidity of symmetric hydrated (bis)glycolate species, which forms in the absence of citric acid, increasing the concentration of symmetric dioxoosmate and arresting the cycle at high pH. Proximal acidic moieties act as a buffer in hydrated (bis)glycolate **ii·H$_2$O** preventing buildup of dioxoosmate **iii**. The equilibrium favors increased concentration of hybrid (bis)glycolate **ii** allowing continuation of the cycle (Scheme 1).

In an effort to find an optimum procedure, cyclic vinyl sulfone **1**, a pivotal aplyronine A intermediate,[6] was subjected to a variety of osmium catalyzed dihydroxylation conditions (Table 1). Entry 1 represents the results of the Upjohn[24] protocol as a point of departure. Consistent with scheme 1, no reaction ensued. It was postulated that substrate insolubility could be an issue in 10:1 H_2O/acetone. Entry 2 employed a THF/water (4:1) system employed by Cho,[25] in the total synthesis of (+)-trans-dihydronarciclasine. The homogenous reaction solution showed no product

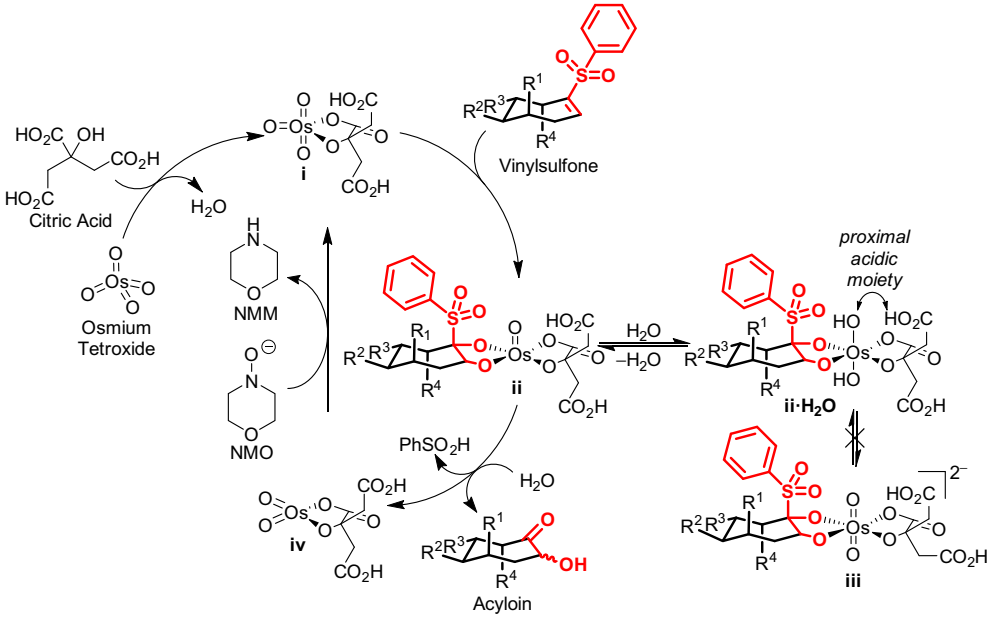
Table 1
Survey of osmium catalyzed dihydroxylation of vinyl sulfones



1 **2**

Entry	Reaction conditions	% Yield[a] (%)	Recovered SM (%)
1	NMO (1.05 equiv), OsO_4 (0.7 mol %), 10:1 H_2O/acetone (0.35 M), rt, 6 h	0	100
2	NMO (2.0 equiv), OsO_4 (1 mol %), 4:1 THF/H_2O (0.05 M), rt, 24 h	0	100
3	NMO (1.10 equiv), $MeSO_2NH_2$ (1.10 equiv), OsO_4 (2 mol %), 10:1 acetone/H_2O (0.1 M), rt, 24 h	35	65
4	NMO (1.10 equiv), OsO_4 (1 mol %), citric acid (0.20 equiv), 4:1 THF/H_2O (0.07 M), rt → 80 °C, 24 h	40	60
5	Citric acid (1.05 equiv), NMO (1.10 equiv), K_2OsO_4 (1 mol %), 4:1 MeCN/H_2O (0.1 M), rt, 24 h	56	35[b]
6	Citric acid (2.05 equiv), NMO (1.10 equiv), K_2OsO_4 (0.10 equiv), 4:1 MeCN/H_2O (0.1 M), rt, 24 h	65	⩽15[b]
7	Citric acid (3.05 equiv), NMO (1.10 equiv), K_2OsO_4 (0.10 equiv), 4:1 MeCN/H_2O (0.1 M), rt, 24 h	73	0[c]

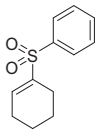
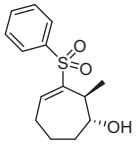
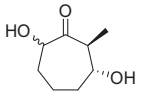
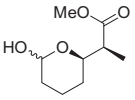
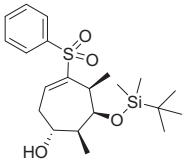
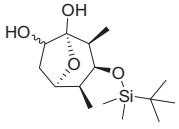
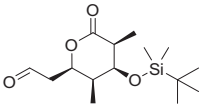
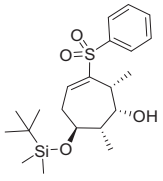
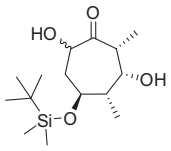
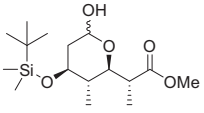
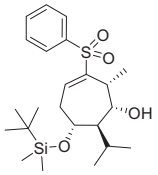
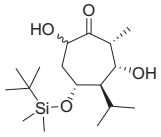
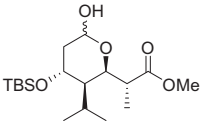
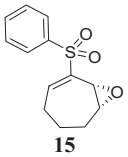
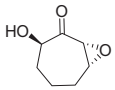
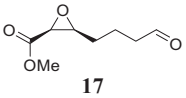
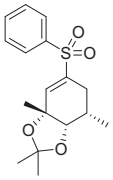
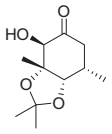
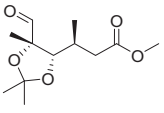
[a] % Yield after column chromatography.
[b] % by NMR analysis.
[c] Conversion of starting material monitored by disappearance of UV activity on TLC.



Scheme 1. Citric acid assisted osmylation of cyclic vinyl sulfones. R^1, R^2, R^3, R^4 = H = Me = OH = OTBS = *i*-Pr.

(**2**) after 24 h by TLC visualization. At this point it was asserted that an additive would be necessary to effect the transformation. Entry 3 utilized methylsulfonamide based upon the Kerr observation of dihydroxylation of an electron deficient dihydrofuran in the total synthesis of (+)-Isatisine A.[26] After 24 h the reaction showed 35% conversion by proton NMR, but an additional 24 h of reaction time showed no further conversion. We next reasoned that the insightful mechanistic work of Sharpless[23] which featured the use of citric acid to stimulate reaction rates would bear fruit. Entry 4 utilizes a substoichiometric amount of citric acid previously employed to successfully dihydroxylate α,β-unsaturated esters, amides, phosphates, and γ,δ-unsaturated sulfones.[23] The reaction ceased after 40% conversion. Heating to 80 °C leads to no further consumption of starting material as evidenced by proton NMR. In entry 5 an increase to 1.05 equiv of citric acid raised the conversion to 56%, but again the reaction did not go to completion. Over the course of the survey it was found that potassium osmate dihydrate was easier to handle and acetonitrile improved the homogeneity of the reaction. The Sharpless protocol used a maximum of 2 equiv of citric acid but using this amount for our substrate returned a remaining 15% starting material (entry 6). We theorized that, due to the possible increased acidity of vinyl sulfone, osmium adducts formed in the catalytic cycle (Scheme 1), were being deprotonated by the NMM amine co-product and/or solvent preventing full

Table 2
Citric acid assisted osmylation and termini differentiated oxidative cleavage of vinyl sulfones

Entry	Vinyl sulfone	Osmylation product[a] (%)	Cleavage product[b] (%)
1	 **3**	 **4** 80%	na
2	 **5**	 **6** *not isolated*	 **7** 85%
3	 **8**	 **9** 95%	 **10** 99%
4	 **1**	 **2** 73%	 **11** 97%
5	 **12**	 **13** 94%	 **14** 87%
6	 **15**	 **16** 97%	 **17** 85%
7	 **18**	 **19** 86%	 **20** 71%/ 76%[c]

[a] $K_2OsO_4{\cdot}2H_2O$ (0. 01 equiv), NMO (2.5 equiv), citric acid (3.0 equiv), 4:1 MeCN/H_2O, rt, 16–24 h.
[b] $Pb(OAc)_4$ (1.5 equiv), MeOH, rt, 5–45 min.
[c] $PhI(OAc)_2$, MeOH (0.1 M), 60 °C, 18 h.

conversion. Apparently increasing the amount of citric acid to 3 equiv (entry 7) provided an equilibrium concentration high enough to neutralize the free amine, thereby establishing a reasonable rate for the osmylation. Complete disappearance of starting material was demonstrated by TLC monitoring and the absence of sulfone signals in the aromatic region of the ^{1}H NMR.

The Purdue group has archived a diverse inventory of cyclic vinyl sulfone polyketide precursors. A selection of these was chosen to explore the optimized citric acid mediated osmylation. Since this study was initiated by real-world need for aldehyde-bearing compounds, lead tetraacetate[27–29] (Pb(IV)OAc) was chosen for oxidative cleavage of the acyloin intermediates. An excellent review by Schmidt and Clark[30] provides a comprehensive survey of reagents for the cleavage of diols and acyloins.

Compound **3** (Entry 1, Table 2) was chosen as an initial example with the fewest variables. The acyloin product (**4**) is well known and provided spectra identical to literature values.[31–34] Oxidative cleavage of the acyloin was previously achieved by Eguchi, Masatomi[35] and Brégeault.[36] Previous studies by the Fuchs group showed facially accessible cyclic vinyl sulfones reactive to osmylation, but facially occluded[17] cyclic vinyl sulfones yielded little product.[26] Compound **5** Entry 2 contains a *trans* stereodiad that was an aplyronine A intermediate.[5,37] The crude epimeric acyloin **6** was subjected to the Criegee oxidation without further purification to yield lactol **7**. The aplyronine A strategy sought to employ cyclic vinyl sulfone stereotetrads as precursors to linear dipropionate segments. Compound **8** (Entry 3) provided target epimeric hydroxy lactol **9** in excellent yields with subsequent cleavage giving 99% yield of **10**. Changing the proximity of the protecting group on Entry 4 afforded desired acyloin **2** epimers in 73% yield. Criegee oxidation provided termini-differentiated epimeric lactol **11** in near-quantitative yield. Compound **12** (Entry 5) is an intermediate prepared for the synthesis of isopropyl discodermolide analogs.[38] Criegee oxidation again smoothly afforded termini-differentiated lactol **14** via **13**.

Early aplyronine A intermediate **15**,[5,7] contains an enantiomerically pure epoxide and provides enantiopure acyloin **16** with the epoxide intact (Entry 6). Criegee oxidation next afforded termini-differentiated epoxide cleavage product **17**. Entry 7, an enantiopure bicyclic cytochalasin C intermediate (**18**),[39–42] accommodates dihydroxylation to **19** and subsequently gives intact acetonide **20** upon oxidative cleavage (Table 2). To address concerns about Pb(IV) toxicity iodobenzene diacetate,[35,43] was also shown to be an efficient oxidative cleavage reagent (Entry 7, case 2).

Conclusions

We have shown that this two-stage osmylation/cleavage protocol is effective on a range of stereorich cyclic vinyl sulfones. Entries 1–5 illustrate tolerance of multiple substitution patterns not previously subject to osmylation. Sterically biased vinyl sulfones such as entries 6 and 7 afford isolable diastereo- and enantiopure acyloins. The inherent dissymmetry of the sulfone-substituted olefin in concert with the presence or absence of a free alcohol moiety dictates formation of either the lactol or lactone product. This method substantially increases the scope of polypropionate construction via vinyl sulfones. Citric acid assisted catalytic osmylation/oxidation is a superior, mild, protection group friendly and convenient alternative for ozonolysis in the vinyl sulfone polypropionate strategy.

It is highly probable that the modified Sharpless conditions used in this study will be applicable for other electronically-deficient olefins.

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Supplementary data

Supplementary data (characterization data and procedures) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.05.044.

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