Relative and Absolute Structure Assignments of Alkenes Using Crystalline Osmate Derivatives for X-Ray Analysis

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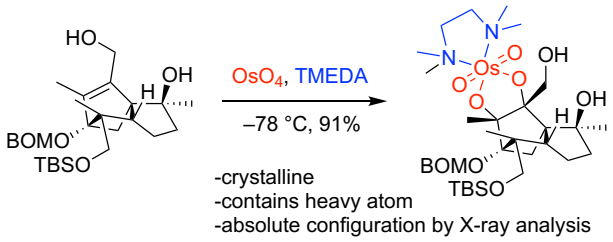
Supporting Information Placeholder



ABSTRACT: Osmium tetroxide and TMEDA form stable crystalline adducts with alkenes. The structure of liquid alkenes can be determined through X-ray analysis of these derivatives. Osmium, a heavy atom, facilitates the crystallographic analysis and the determination of the absolute configuration using common Mo X-ray sources. The utility of this method for assigning structures and absolute configurations was demonstrated on a number of unsaturated substrates that include simple alkenes, enones, enol ethers, and silyl enol ethers.

Determination of absolute configuration of organic molecules can be challenging. Numerous strategies have been developed to solve this problem,[1] including experimental and computation ECD and VCD approaches,[2] derivatization strategies such as the preparation of Mosher's esters or amides,[3] and exciton coupled circular dichroism (ECCD).[4] Our lab has developed the competing enantioselective conversion method, which is expeditious, but requires a firm understanding of the reactivity for an amine or alcohol substrate.[5] X-ray crystallography is the gold standard because it not only determines the absolute configuration (using anomalous dispersion), but also confirms the structure assignment. Unfortunately, most organic compounds are not crystalline. Many derivatization strategies have been developed to generate crystalline compounds from organic liquids, but they can be unreliable and labor intensive. In a remarkable development, absorption of a liquid sample into a crystalline matrix for X-ray analysis has recently been reported.[6] We have developed a new approach based on the osmylation of alkenes and subsequent crystallization of these osmate esters. This osmylation strategy is useful for both the assignment of absolute configuration, as well as the assignment of the relative structure of alkenes.[7]

Many derivatization tactics have been used to improve the crystallinity of organic compounds. Alcohols or amines have been derivatized with 4-nitrobenzoyl chloride or 4-bromobenzoyl chloride. Ketones and aldehydes have been transformed into 3,5-$(NO_2)_2$-phenylhydrazones. Carboxylic acids are often crystallized as amine salts. Ferrocene carboxylic acid forms esters and amides that are highly crystalline.[8] They also contain a heavy atom (Fe) that facilitates the measurement of anomalous dispersion and assignment of absolute configuration by Flack's method using common molybdenum X-ray sources.[9] Further improvements in the Flack method allows it to be applied to molecules that contain no heavy atoms,[10] most often with a Cu X-ray source. High quality crystals are required for the diffraction analysis. Very recently, sulfate derivatives of alcohols have been crystallized as guanidinium salts and analyzed by crystallography.[11] The use of crystalline derivatives has rendered X-ray analysis feasible for many organic compounds.

We recently faced the problem of assigning the absolute configuration of the natural product illisimonin A.[12] Synthesis of racemic illisimonin A confirmed the relative configuration of the assigned structure, but an enantioselective route was necessary to determine the absolute configuration. We eventually solved the problem by resolving an alcohol intermediate using (*S*)-1-(1-naphthyl)ethyl isocyanate and separating the diastereomers by chromatography, Figure 1. Carbamate **1** was carried on to natural (–)-illisimonin A. Carbamate **2** was elaborated to a crystalline derivate **3** using ferrocene carboxylic acid, and the absolute configuration was determined by X-ray analysis. A crystalline derivative was only found after we carried the material through five steps, which included removal of the TBS

and BOM protecting groups. The data led to a revision of the absolute configuration of the natural product.

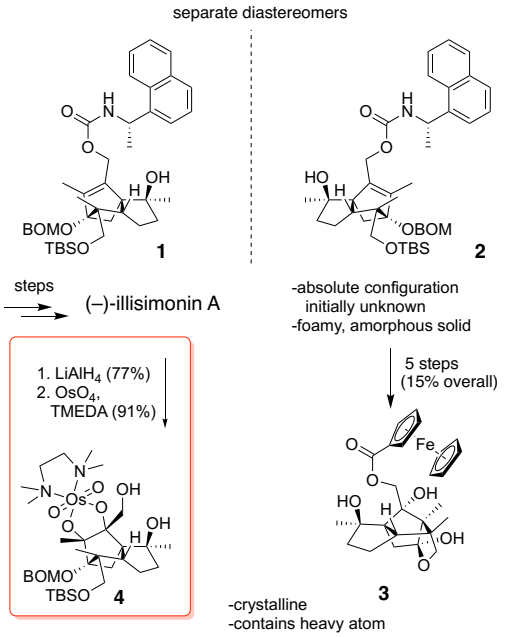


Figure 1. Determination and revision of the absolute configuration of (–)-illisimonin A. Our published assignment was based on ferrocene ester **3**, whose absolute configuration was determined through X-ray crystallography. Osmate ester **4**, prepared in fewer steps and still carrying protecting groups, was analyzed by crystallography and provided a more direct means to assign the absolute configuration of the natural product.

While ferrocene carboxylate **3** crystals were analyzed, we attempted another derivatization strategy. Donohoe reported that OsO_4 and TMEDA (tetramethylethylenediamine) make a very reactive complex, estimated to be 100 times more reactive than the OsO_4-pyridine complex, that rapidly dihydroxylates alkenes.[13] The OsO_4-TMEDA complex can be directed by hydrogen bonding and frequently reacts with good diastereoselectivity.[13] The resulting osmate esters were remarkably stable, and Donohoe determined the structures of a few of the products by crystallography.[13] With little to lose and still uncertain of the outcome with crystals of **3**, we osmylated the alcohol derived from carbamate **1**. This experiment directly led to a crystalline derivative **4**. Remarkably, this chromatographically stable osmate ester contained both a TBS and BOM group, which often limit crystallinity, and yet it formed X-ray quality crystals. The resulting X-ray structure (Figure 2) confirmed the revised absolute configuration of (–)-illisimonin A.

X-ray structures of crystalline osmate esters have been reported in the literature. Where the organic component was non-trivial, the crystalline osmates were used to elucidate the stereoselectivity of the osmylation reaction,[13,14] the regioselectivity of the reaction,[15] or to help explain the effect of chiral ligands in stoichiometric enantioselective osmylations.[16] Several studies investigating the interactions of OsO_4 with RNA and DNA have produced crystal structures of nucleoside and nucleotide-derived osmates.[17] Recently X-ray analysis of osmates derived from porphyrins have demonstrated the position of reaction.[18] These structures demonstrate that osmate esters prepared from a wide variety of alkenes will form X-ray quality crystals for analysis. We are aware of only one case where X-ray crystallography of an osmate ester was used to assign the structure of the unsaturated organic component.[19] We propose that TMEDA-osmate esters, highly crystalline derivatives of alkenes, can be used to assign relative and absolute structures of starting alkenes. Although the cost and toxicity of OsO_4 is a concern for preparative, stoichiometric reactions, generating osmates for X-ray structure analysis is best done on small scale, where the cost is negligible and safety issues are easily managed.

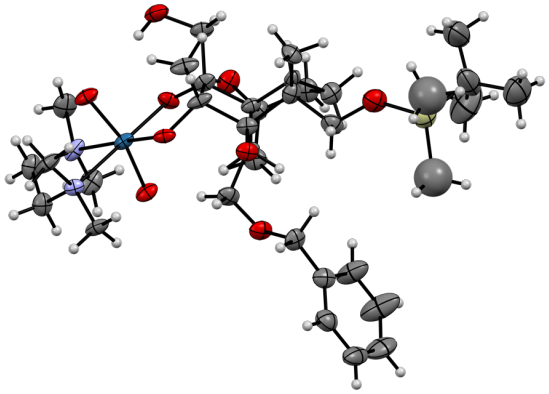


Figure 2. X-ray Structure of osmate **4**. The osmium is a distorted octahedron with local C_2 symmetry. The crystals incorporate THF (not shown) in the unit cell. Solvent incorporation was found with most osmate ester crystals in Table 1.

To evaluate the utility of this method, we initially examined commercially available, liquid alkenes. The results are shown in Table 1. The osmylation of prenol (**5a**), geraniol (**6a**), and (+)-2-carene (**7a**), all proceeded in good yield and were purified using flash column chromatography (CH_2Cl_2/MeOH) on silica. The solid products were readily crystallized using vapor diffusion, and their structures determined by single crystal X-ray diffraction. For geraniol, osmylation occurs proximal to the allylic alcohol, in accord with the hydroxyl-directing effect reported by Donohoe.[13] The melting point of the geraniol osmate **6b** is 61 °C higher than the corresponding ferrocene carboxylate ester, indicating enhanced crystallinity.[8] In the case of (+)-2-carene osmate **7b**, the absolute configuration was confirmed by the Flack method.[9]

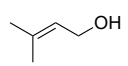
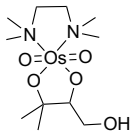
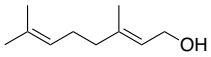
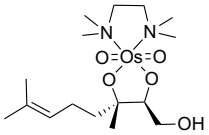
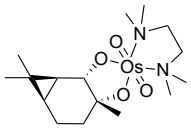
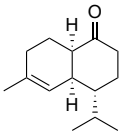
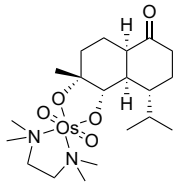
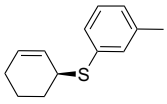
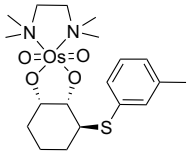
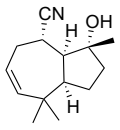
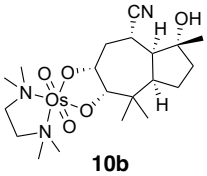
Decalin **8a**[20] and allylic sulfide **9a**[21] are both oils. They react under standard conditions (OsO_4 and TMEDA at –78 °C in CH_2Cl_2) to form osmate esters in good yields. The structures and absolute configurations were determined by X-ray crystallography. Sulfide **9a** is a compelling example of the utility of our methodology. Its absolute configuration was originally inferred by analogy to a model substrate synthesized using the same enantioselective method. From 14 mg of the sulfide, we prepared 36 mg of the osmate ester that crystallized on the first attempt, providing conclusive experimental evidence of its proposed absolute configuration.

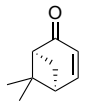
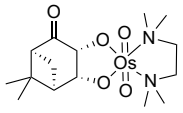
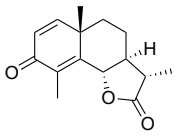
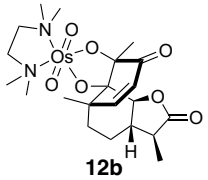
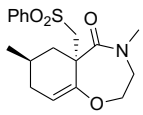
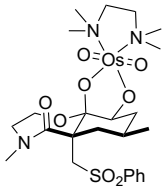
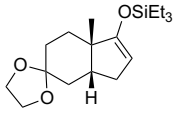
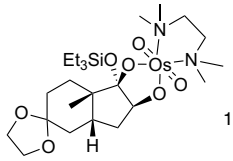
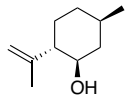
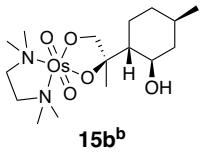
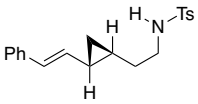
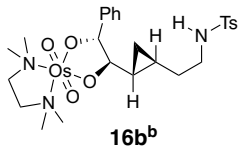
Alkene **10a**[22] reacted with the osmium complex selectively and the adduct **10b** crystallized readily. Initially the crystals were twinned, which made assigning absolute configuration challenging. Fortuitously, changing crystallization solvent systems resolved the twinning, and the absolute configuration could be confidently assigned.

Verbenone (**11a**), an oil, and the solid dienone α-santonin (**12a**) were both osmylated and the adducts readily crystallized, highlighting the method's applicability to electron deficient alkenes. The chemoselectivity of the OsO_4/TMEDA system in the osmylation of α-santonin was notable, as a lack of selectivity could lead to lower yields and perhaps necessitate further purification.[23] The selectivity of OsO_4 additions has been extensively documented.[24]

The dihydroxylation of enol ethers and silyl enol ethers typically leads to isolation of alpha hydroxy ketones.[25] We sought to investigate whether the osmate esters of these motifs would be kinetically stable and crystalline. Enol ether **13a** formed a stable, crystalline osmate ester. Even silyl enol ether **14a** formed a moderately stable osmate ester. While we did note some unidentified decomposition over time, the TES ether osmate **14b** could be crystallized directly from the crude reaction mixture, without prior chromatography.[26]

Table 1. Alkenes and the Derived Crystalline Osmate-TMEDA Esters[a]

Alkene	Yield	Osmate	mp
 **5a** achiral oil	59%	 **5b**	135 °C (dec)
 **6a** achiral oil	60%	 **6b**	100-103 °C
 **7a** enantiopure oil	85%	 **7b**	180 °C (dec)
 **8a** racemic oil	93%	 **8b**	87-92 °C
 **9a** enantiopure oil	91%	 **9b**	170 °C (dec)
 **10a** enantiopure solid mp = 59-63 °C	97%	 **10b**	231 °C (dec)

Alkene	Yield	Osmate	mp
 **11a** enantiopure oil	81%	 **11b**	192 °C (dec)
 **12a** enantiopure solid mp = 172 °C	87%	 **12b**	202 °C (dec)
 **13a** racemic oil	76%	 **13b**	182–185 °C
 **14a** enantiopure oil	-	 **14b**	170 °C (dec)
 **15a** enantiopure oil	87% 1.3:1	 **15b**[b]	84–87 °C
 **16a** racemic oil	68% 2.4:1	 **16b**[b]	90-93 °C

[a]Standard conditions: 1.0 equiv alkene and 1.1 equiv TMEDA, CH_2Cl_2, –78 °C, then add 1.0 equiv OsO_4, 60 min. [b]The diastereomeric mixture of osmate esters was separated by chromatography on silica gel prior to crystallization.

One drawback of the functionalization of alkenes is the possible generation of diastereomers. Initially, we investigated substrates that gave high diastereoselectivity. In theory a single diastereomer could be selectively crystallized out of a mixture, but we did not have much success with roughly equimolar mixtures of diastereomeric osmates. However, we were able to separate diastereomeric osmates when the osmate group was proximal to the other stereocenters. Thus, (–

)-isopulegol (**15a**) and vinyl cyclopropane **16a** were osmylated to form diastereomeric mixtures. The osmate esters were separated by silica gel chromatography prior to crystallization.

Several alkenes did not result in useful osmate crystals, and these cases are presented in Table S1 in the supporting information. Several were unreactive with OsO_4-TMEDA, including a benzothiophene. A chloroalkene did react, but the osmate was not stable. A few examples formed stable osmates, but did not crystallize in our hands. In one case, diastereomeric osmate esters were inseparable by chromatography. The osmate derivatization and crystallization strategy was successful for most but not all substrates.

Derivatization of alkenes with OsO_4-TMEDA is a mild and efficient procedure. It offers a tactically distinct alternative from traditional functionalization strategies which rely on alcohols, amines, ketones, and carboxylic acids. The examples in Table 1 demonstrate that the reaction is compatible with alcohols, cyclopropanes, ketones, sulfides, nitriles, acetals, lactones, amides, sulfones and silyl ethers. Dichloromethane is the standard solvent, but reactions run in THF and MeOH gave >80% yields from verbenone (**11a**), demonstrating that more polar substrates could be derivatized under these conditions. The reagents add 370 au to the alkenes. For precious samples, the increase in mass of the osmate esters simplifies crystallization.

We have demonstrated that OsO_4-TMEDA reacts with a variety of alkenes, and the resulting osmate esters are crystalline and suitable for X-ray diffraction in most cases. The osmium contained within these complexes facilitates the assignment of absolute configuration by increasing anomalous scattering. When mixtures of diastereomeric osmates are generated, chromatographic separation is often possible. The derivatization of alkenes as OsO_4-TMEDA adducts and X-ray crystallographic analysis will be a useful new tool for the assignment of structure and absolute configuration.[27]

ASSOCIATED CONTENT

Supporting Information

Experimental details, compound characterization and crystallization methods are provided for all osmate esters. CIF files and crystallographic analysis are included. The Supporting Information is available free of charge on the ACS Publications website.

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Author Contributions

The manuscript was written through contributions of all authors.

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