Asymmetric Catalysis

Oxidative Cyclization of Diols Derived from 1,5-Dienes: Formation of Enantiopure *cis*-Tetrahydrofurans by Using Catalytic Osmium Tetroxide; Formal Synthesis of (+)-*cis*-Solamin**

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In 1965, Klein and Rojahn discovered that treatment of 1,5-hexadiene with $KMnO_4$ afforded *cis*-2,5-bis(hydroxymethyl)-tetrahydrofuran.[1] The mechanism of the reaction was a matter of some debate but eventually was considered to be a concerted cyclization of a metal–glycolate complex across a distal alkene.[2] This mechanism is consistent with the fact that the addition across both alkenes is stereospecific (*syn*) and also that stereoselective formation of *cis*-tetrahydrofurans is observed. Since the original reports using $KMnO_4$, several

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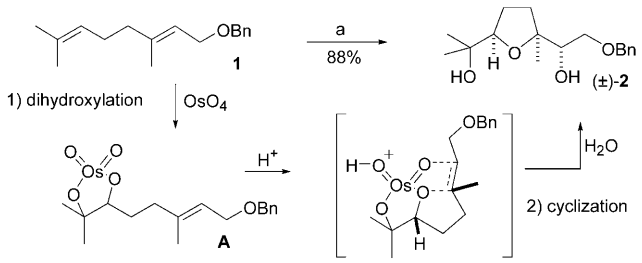
other metals have been shown to mediate this type of cyclization, including ruthenium[3] and, more recently, osmium.[4]

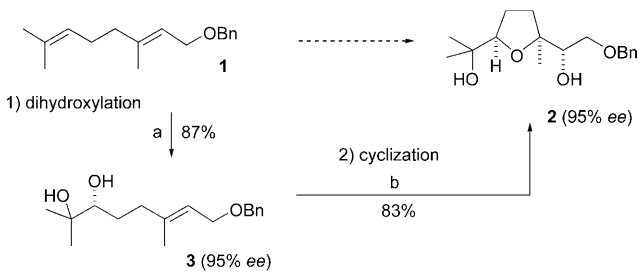
We recently described the development of the oxidative cyclization of 1,5-dienes using catalytic amounts of OsO_4 (5 mol%) under acidic conditions (see **1**→**2**, Scheme 1).[5] This sequence is remarkable for its high yields, especially during the oxidation of mono- and disubstituted alkenes, which tend to give overoxidation products with manganese and ruthenium oxidants.



Scheme 1. Oxidative cyclization of 1,5-dienes. Reagents and conditions: a) OsO_4 (5 mol%), Me_3NO (4 equiv), camphor sulfonic acid (6 equiv), CH_2Cl_2. Bn = benzyl.

A major obstacle to the application of this sequence in synthesis is the fact that racemic mixtures are produced. Attempts to introduce asymmetric induction into this reaction by the addition of chiral amine ligands failed, presumably because the pH values of the solutions were too low to enable efficient coordination of the amines to the osmium center. However, we now report a reaction sequence that overcomes this hurdle, allows the formation of tetrahydrofuran (THF) systems with complete control over both the relative and absolute stereochemistries, and uses catalytic amounts of a transition metal. We have discovered that vicinal diols derived from 1,5-dienes will cyclize to form the THF ring system when they are subjected to oxidative cyclization conditions (see **3**→**2**, Scheme 2). This cyclization reaction becomes a powerful methodology because the starting diols can be obtained from 1,5-dienes in a regio- and stereoselective manner by using, for example, the Sharpless asymmetric dihydroxylation (AD) reaction.[6] We have proven unambiguously by HPLC analysis that there is no loss of stereochemical integrity during the cyclization process.

The cyclization of diol **3** gave **2**, which was identical to the product obtained from the corresponding diene. This result



Scheme 2. Two-step procedure for the formation of enantiopure *cis*-THF rings. Reagents and conditions: a) AD-mix-β; b) OsO_4 (5 mol%), Me_3NO (4 equiv), trifluoroacetic acid (TFA; 6 equiv), acetone/H_2O, RT.

suggests that the 1,2-diol forms a chelated osmate ester in situ (see intermediate **A**, Scheme 1) that then cyclizes as before.

Naturally, we were intrigued by the oxidation state of the osmium center in **A**, because the diene cyclization protocol provides Os^{VI} directly and the diol cyclization route commences with Os^{VIII}.[7] Therefore, we examined the role of additives in the cyclization of **3** (Table 1) and found that a range of

Table 1: Oxidation of (+)-**3**→(−)-**2**.

Entry	Sacrificial alkene[a]	*t* [h]	Conversion [%][b]
1	none	6	30
2	none	30	85 (55)
3	cyclohexene (5)	6	40
4	cyclohexene (5)	30	100 (83)
5	isoprene (5)	6	45

[a] Equivalents given in brackets. [b] Yield of isolated product given in brackets.

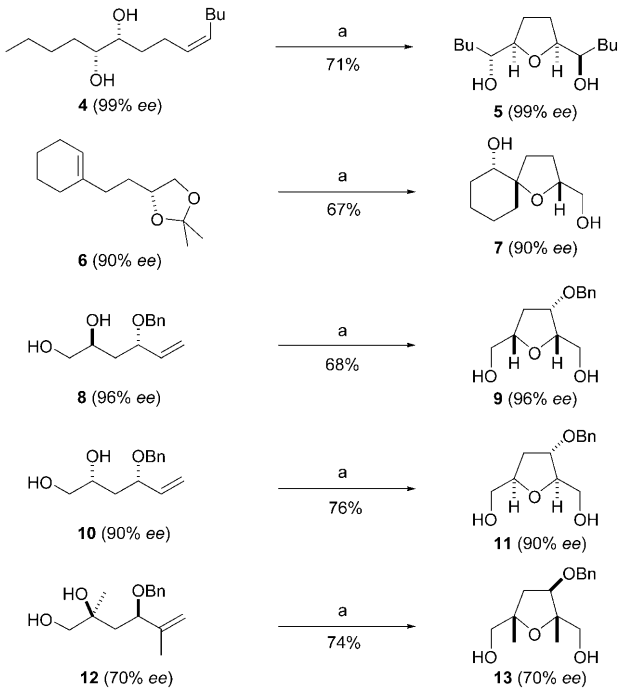
sacrificial alkenes improved the yield (5 equiv were best). It is possible that this second alkene is able to generate Os^{VI} in situ (from Os^{VIII}) by a dihydroxylation reaction and thus acts to increase the amount of active Os^{VI} catalyst in the reaction mixture.

Although we could find no advantage to using cyclohexene rather than isoprene, the choice of sacrificial alkene becomes important in the purification as the product occasionally coelutes with the diol derived from this second alkene.

This investigation is related to the oxidative cyclization of bishomoallylic alcohols using Re^{VII} reagents (to give *trans*-tetrahydrofurans)[8] and diols using Cr^{VI} reagents[9] (the yields for this process are low), which have both been used successfully in synthesis.[10] However, both sets of conditions use stoichiometric amounts of the metal reagent to accomplish these transformations, and the advantages of catalytic metal oxidants are clear.

Next, we examined the oxidative cyclization of a range of diols derived from 1,5-dienes (Scheme 3). The diol starting materials were made by a regio- and stereoselective dihydroxylation of a diene by using the Sharpless AD reaction—although there are other viable routes to the diol precursors. The cyclization was shown to be tolerant of a variety of different substitution patterns on the alkene, diol unit, and even the backbone (Scheme 3). The yields were good and the products from the diol cyclizations were identical, as shown by NMR spectroscopic analysis, to a (racemic) compound formed by the cyclization of the corresponding 1,5-diene under the conditions shown in Scheme 1. As expected, the sequence is highly selective in each case for the formation of *cis*-tetrahydrofurans. Moreover, the enantiomeric purity of the diol was transferred completely to the THF product.

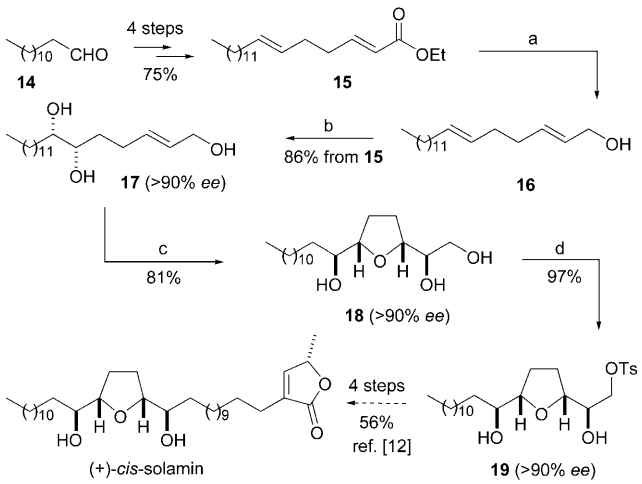
We then sought to exemplify this new cyclization reaction in synthesis. Our target was *cis*-solamin, which is an annonaceous acetogenin with potent biological activity (e.g., *cis*-solamin displays cytotoxicity and hemolytic activity).[11,12] Brown and co-workers[12] recently reported a clever synthesis of this molecule, whereby $KMnO_4$ was used to oxidatively cyclize a 1,5-diene precursor that was loaded with a chiral



Scheme 3. Oxidative cyclization of various diols. Reagents and conditions: a) OsO_4 (5 mol%), Me_3NO (4 equiv), TFA (6 equiv), acetone/H_2O, RT. Isoprene (5 equiv) was used as an additive in each entry, except for **4** in which cyclohexene was used.

auxiliary to control the absolute stereochemistry of the product.

This literature route was used to prepare compound **15** in four steps (Scheme 4). The ester group was then reduced and a regioselective AD reaction was performed on hydroxy-substituted diene **16** to yield **17** in 86% yield from **15** and with >90% *ee*. The key oxidative cyclization reaction of **17** worked well and gave THF product **18** in 81% yield. This product was subsequently transformed into tosylate **19** (>90% *ee* as determined by HPLC), which was spectroscopically identical to the product reported by Brown and co-workers. This investigation constitutes a formal synthesis of the target as **19** can be converted into (+)-*cis*-solamin in four steps and 56% yield by using a literature precedent.[12] This osmium-catalyzed oxidation methodology compares well with the permanganate-based alternative (e.g., **15**→**18**: obtained in five steps and 46% overall yield from the method of Brown and co-workers[12] compared with three steps and 70% overall yield from our new approach).



Scheme 4. The synthesis of *cis*-solamin. Reagents and conditions: a) diisobutylaluminum hydride; b) AD-mix-α,$(DHQ)_2PHAL$; c) OsO_4 (5 mol%), Me_3NO (4 equiv), TFA (6 equiv), isoprene (5 equiv), acetone/H_2O, RT; d) Bu_2SnO, *p*-toluenesulfonyl chloride (TsCl), benzene. $(DHQ)_2PHAL$ = hydroquinine 1,4-phthalazinediyl diether.

To conclude, we present herein a new catalytic oxidation reaction that promotes the cyclization of vicinal diols onto a proximal alkene with a high level of stereocontrol. The diol precursors are readily prepared as single enantiomers, which means that the oxidation products (tetrahydrofurans) can also be accessed in enantiopure form. This method is simple to perform, high yielding, and tolerant of substitution on the THF backbone. The usefulness of this method has been proved in a short and extremely efficient (formal) synthesis of (+)-*cis*-solamin.

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