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Osmium-Mediated Oxidative Cyclizations: A Study into the Range of Initiators That Facilitate Cyclization

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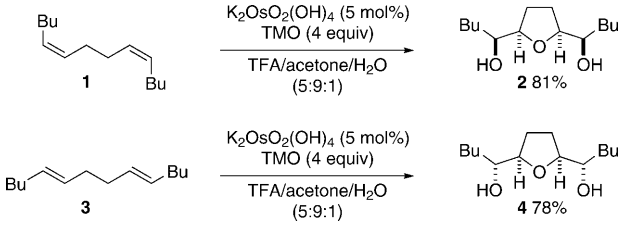
Abstract: A general route to prepare substituted, saturated five-membered heterocycles has been developed. The application of a wide range of starting materials to the osmium-catalyzed oxidative cyclization reaction is described. Diols, hydroxy-amides, hydroxy-sulfonamides, and carbamates all cyclize in moderate to excellent yields to give *cis*-tetrahydrofurans and pyrrolidines, depending upon the position of the heteroatoms in the starting materials. These cyclizations all proceed with near total selectivity for the *cis*-heterocycles, and with stereospecific introduction of a hydroxy group adjacent to the ring. Moreover, routes to enantiopure starting materials are described, which give enantiopure products upon cyclization. Catalyst loadings of as low as one mol percent have been successfully employed for this transformation.

Keywords: catalysis · heterocycles · osmium · pyrrolidines · tetrahydrofurans

Introduction

The oxidative cyclization of 1,5-dienes to give 2,5-disubstituted *cis*-tetrahydrofurans (THFs) has received a considerable amount of attention since its discovery by Klein and Rojahn in 1965, with a number of metal-oxo species now capable of accomplishing this transformation.[1] Recent work from our laboratory has shown that catalytic osmium tetroxide in the presence of trimethylamine *N*-oxide (TMO) and trifluoroacetic acid (TFA) was a mild and effective system for the oxidative cyclization of 1,5-dienes (Scheme 1).[2] This reaction was stereoselective for the formation of *cis*-heterocycles and stereospecific with respect to alkene oxidation, as confirmed by X-ray crystal structure analysis on the cyclized compound **2**.



Scheme 1. Catalytic oxidative cyclization of 1,5-dienes. TMO = trimethylamine *N*-oxide dihydrate.

The proposed mechanism for this transformation involved osmylation of a single alkene unit, followed by an acid-promoted cycloaddition of the osmate ester to give the corresponding THF via transition structure **5** (Figure 1). This was analogous to the mechanism proposed by Piccialli et al.[1k] and in accordance with the mechanism of permanganate-mediated oxidative cyclization originally proposed by Baldwin et al.[1c]

The bidentate nature of the initially formed osmate ester enforced the 2,5-*cis* selectivity of the cyclization, because models indicated that such a bidentate osmate ester species could not attain sufficient orbital overlap with the alkene to

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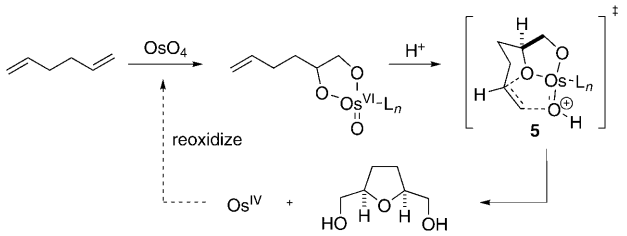


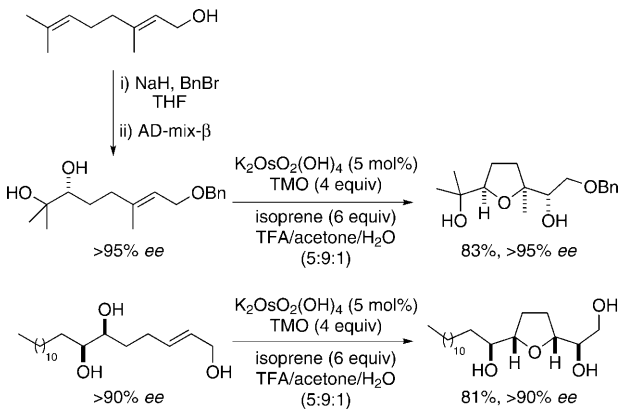
Figure 1. Proposed mechanism for catalytic oxidative cyclization (likely osmium oxidation states shown).

give the *trans*-product (see **5**); furthermore, the related rhenium(VIII) oxide mediated cyclizations of 5-hydroxyalkenes, proposed to proceed via a monodentate rhenium ester, afforded 2,5-*trans*-THFs owing to an "open" transition state.[3]

However, the diene cyclization reaction offered no scope for the synthesis of enantiopure THFs. Addition of cinchona alkaloid ligands to a catalytic oxidative cyclization led to no absolute stereochemical induction, likely owing to the low pH leading to protonation of the chiral amine ligand and possibly also to the initial dihydroxylation step being a ligand-independent, second-cycle process.[4] A range of pH values and oxophilic Lewis acids were screened in the oxidative cyclization reaction in a search for acidic conditions that would activate the metal-oxo species but not deactivate the amine, but to no avail.

We then uncovered an analogous oxidative cyclization utilizing enantiopure diols, derived from 1,5-dienes by Sharpless asymmetric dihydroxylation, to afford enantiopure THFs with no erosion of enantiomeric purity (Scheme 2).[5] This transformation greatly improved the scope of the oxidative cyclization, especially with respect to the formation of single product enantiomers, and was subsequently employed in the synthesis of the natural products *cis*-solamin and *cis*-sylvaticin.[6]

During these studies, it was found that an excess of a sacrificial alkene (isoprene shown in Scheme 2) in the reaction mixture ensured high yields and satisfactory reaction times.[5a] We postulated that this second alkene was dihydroxylated in situ to prevent unwanted dihydroxylation of the substrate olefin, a process clearly detrimental to the yield of THF (see below). Herein, we report a full account of our investigations into different initiating functionalities for osmium in the oxidative cyclization reaction for the formation of both oxygen and nitrogen heterocycles. The aim of these studies was to increase the scope of the oxidative cyclization to encompass new functionality adjacent to the THF ring, and also to investigate cyclization to form pyrrolidines through a completely new mode of reaction.

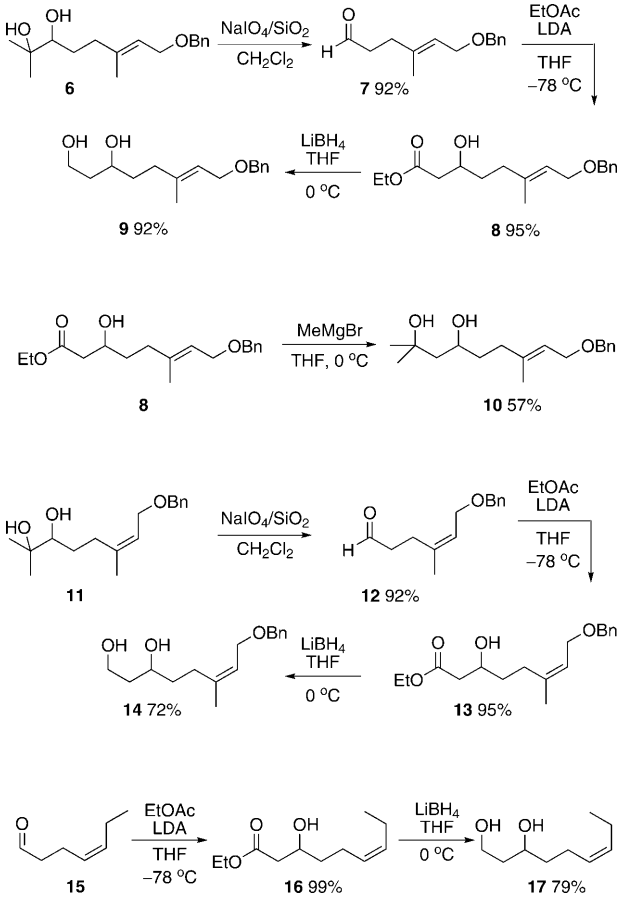


Scheme 2. Oxidative cyclization of enantiopure diols.

Results and Discussion

Oxidative Cyclization of 1,3-Diol Initiators

Initially, we chose to examine the oxidative cyclization of 1,3-diols to give the corresponding *cis*-THFs. Success in this endeavor would expand the range of functionalities that chelate to osmium and facilitate cyclization, increasing the number of structural units accessible from this methodology. Therefore, the starting 1,3-diols were synthesized from the corresponding aldehydes by aldol reaction and subsequent reduction or organometallic addition (Scheme 3). Thus, the known aldehyde **7** was synthesized from diol **6** (derived in

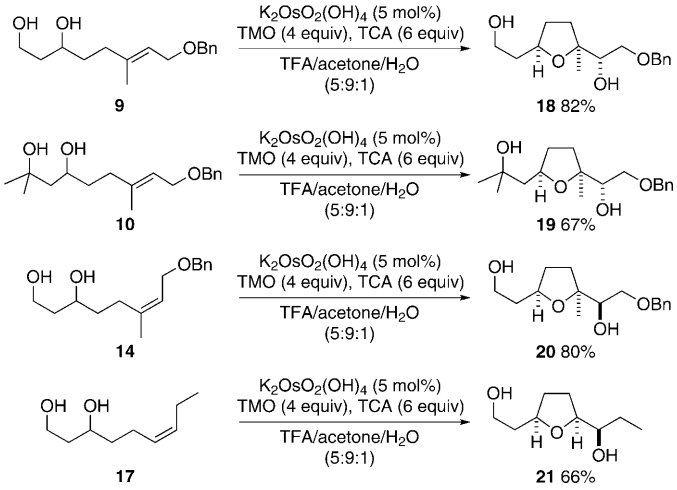


Scheme 3. Synthesis of 1,3-diol substrates for oxidative cyclization. LDA = lithium diisopropylamide.

two steps from geraniol)[7] by oxidative cleavage with sodium periodate in 92% yield. Subsequent aldolizaton with the lithium anion of ethyl acetate gave the hydroxy-ester **8** in good yield. Lithium borohydride reduction to the 1,3-diol **9** proceeded in 92% yield, while the addition of an excess of methylmagnesium bromide furnished the tertiary alcohol **10** in 57% yield. In order to probe the stereospecificity of the cyclization reaction, the corresponding 1,3-diol **14** bearing a *cis*-alkene was prepared by the same sequence, beginning with the known diol **11** derived from nerol.[8] A second 1,3-diol **17** was readily prepared from commercially available *cis*-4-heptenal (**15**) in two facile steps (Scheme 3).

During optimization studies on the attempted cyclization of 1,3-diol **9**, the reaction was found to be much more sluggish than for the corresponding 1,2-diol using isoprene as a sacrificial alkene, with only 40–50% product being obtained even after 36–48 h. This difference in reactivity was attributed to the weaker chelating ability of 1,3-diols over 1,2-diols for large metals such as osmium (larger metals generally have a preference for five-membered chelates over six, owing to more favorable bond angles).[9] A consequence of this weaker binding would be a lower concentration of the "loaded" 1,3-diol osmate ester and, therefore, a slower overall reaction. In order to try to speed up catalytic turnover of any osmium that was bound to the 1,3-diol, we proposed the use of a sacrificial alkene bearing a neighboring group capable of assisting with hydrolysis and ligand exchange after cyclization. We reasoned that an increase in the turnover of the catalyst might compensate for the poorer binding of the 1,3-diol and thereby increase the overall reaction rate. Sharpless and Fokin had shown previously that addition of citric acid to otherwise slow dihydroxylation reactions can lead to a dramatic rate increase, owing to the free carboxylate group of the citrate ligand assisting with hydrolytic release of the product.[10] α,β-Unsaturated carboxylic acids also undergo rapid aminohydroxylation for the same reason, and the amino alcohol products are excellent ligands for accelerating both aminohydroxylation and dihydroxylation reactions.[11] As a result, it was proposed that an α,β-unsaturated carboxylic acid would be a suitable sacrificial alkene, since the resulting bound diol (derived from dihydroxylation) should allow faster exchange with the 1,3-diol substrate and hydrolytic release of the product, effectively acting as a second cycle ligand. Pleasingly, the use of *trans*-cinnamic acid (TCA) resulted in a significant increase in rate (complete consumption of starting material was observed after 16–24 h) for the cyclization of 1,3-diol **9** (Scheme 4), while control experiments showed that this rate increase was unlikely to be derived from the simple pH effects of adding extra acid to a cyclization.[12] Application of these optimized reaction conditions to the cyclization of 1,3-diols **9**, **10**, **14**, and **17** delivered the THFs **18**–**21** in 66-82% yield as single product diastereomers (by ^{1}H and ^{13}C NMR).

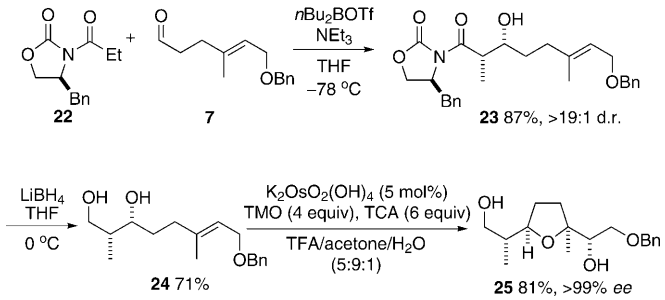
Nuclear Overhauser effect (nOe) experiments on **18**–**21** showed that the THFs had a 2,5-*cis* relationship, and the differences in the NMR spectra of **18** and **20** indicated that the reaction was stereospecific with respect to addition across



Scheme 4. Oxidative cyclization of 1,3-diols. TCA = *trans*-cinnamic acid.

the alkene unit. Given these observations, and the substantial precedent that exists for this oxidative cyclization reaction, we make the reasonable assumption that addition across the alkene is *syn* and the stereochemistry is therefore as shown in Scheme 4.

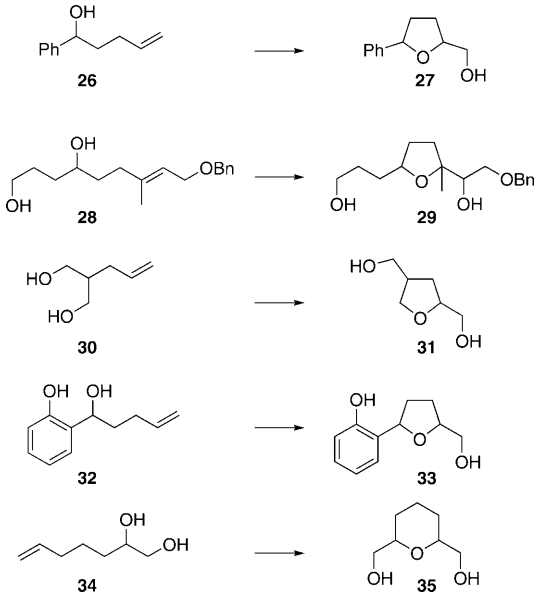
Next, we sought to prepare and test an enantiopure 1,3-diol in the oxidative cyclization reaction (Scheme 5). Thus, aldehyde **7** underwent efficient aldolization with Evans auxiliary **22**[13] in the presence of nBu$_2$BOTf and triethylamine to give the *syn*-aldol product **23** in 87% yield. After reductive removal of the auxiliary, the diol **24** was subjected to the optimized cyclization conditions and yielded 81% of the desired hydroxy-THF **25** (Scheme 5).



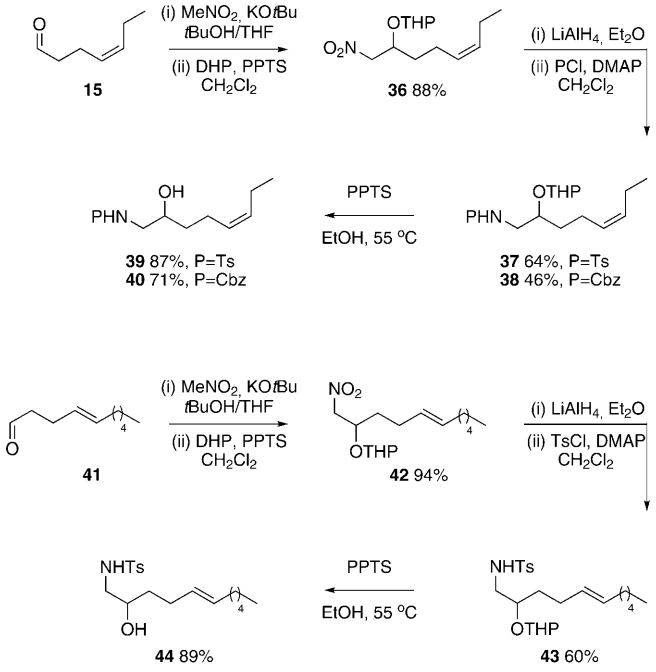
Scheme 5. Synthesis and cyclization of an enantiopure 1,3-diol substrate.

Limitations to the Methodology

Subsequently, a series of other initiator groups were investigated in the oxidative cyclization reaction (Scheme 6). In the first instance, a number of compounds were prepared which did not give the expected heterocycles under the conditions developed. Bis homo-allylic alcohol **26** failed to cyclize under a variety of osmium-catalysis conditions, in contrast to the procedures documented for rhenium and cobalt.[14] The formation of a seven-membered osmate ester derived from **28** was assumed to be unlikely, given the rela-



Scheme 6. Limitations of diol cyclizations. In each case, a variety of different cyclization conditions (based around catalytic osmium, acid, reoxidant, and solvent) were screened.

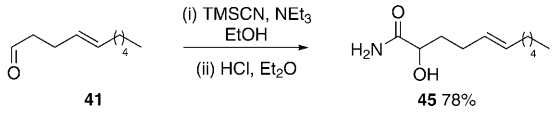


tive unreactivity of **9**. Moreover, the osmate ester derived from 1,3-diol **30** suffered from undue strain, which made overlap of the olefin with an osmium-oxo ligand difficult and prohibited cyclization. The lack of reactivity of phenol **32** was perhaps more puzzling, but demonstrated that planarity along the 1,3-diol backbone was not tolerated in this reaction. Finally, the failure of the 1,2-diol **34** to cyclize to the corresponding tetrahydropyran **35** under a variety of different conditions (some forcing) was surprising, and attributed to excessive steric strain in the transition state.[15]

Formation of Amino-THFs by Oxidative Cyclization

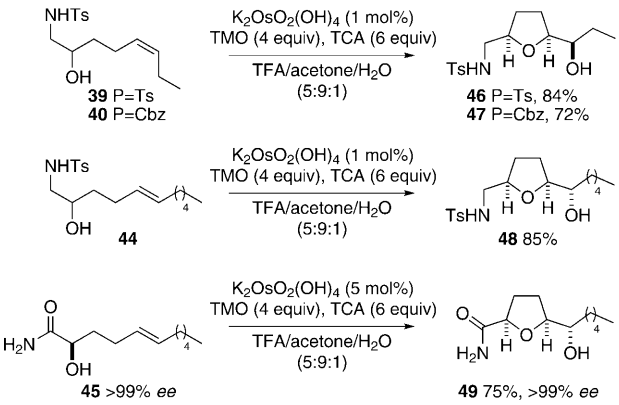
Having shown that dienes, 1,2-diols, and 1,3-diols were suitable initiators for the oxidative cyclization reaction, attention was then turned to protected amino alcohols. Sharpless' work on second-cycle ligands for dihydroxylation indicated that such substrates were good ligands for osmium, and the fact that catalytic aminohydroxylation was possible indicated that the binding constants should not be so high as to preclude useful catalyst turnover.[16]

Amino alcohols **39** and **40** were both synthesized in five steps from commercially available *cis*-4-heptenal (**15**) in 49% and 29% overall yields, respectively.[12] Thus, Henry reaction, alcohol protection, nitro reduction, and amine protection, all followed by alcohol deprotection, provided a facile route to these compounds (Scheme 7). Similarly, amino alcohol **44** was synthesized from commercially available *trans*-4-decenal (**41**) in 50% overall yield utilizing the same five-step sequence. The hydroxy-amide **45** was also constructed from **41** and resolved by separation of its Mosher's ester derivatives to furnish enantiopure material.[12]



Scheme 7. Synthesis of amino alcohols **39**, **40**, **44**, and **45** (Mosher's ester formation from alcohol **45** and subsequent separation of diastereomers furnished enantiopure samples of **45**). DHP = dihydropyran; Ts = toluene-4-sulfonyl; Cbz = benzyloxycarbonyl; PPTS = pyridinium *para*-toluene sulfonate; DMAP = 4-dimethylaminopyridine; THP = tetrahydropyran.

Pleasingly, submission of the sulfonamide and carbamate protected amino alcohols **39**, **40**, **44**, and **45** to the optimal conditions for 1,3-diol cyclization led to excellent yields of the corresponding amino-THFs **46**–**49** (Scheme 8). X-ray crystal structure analysis of **46** and **48** indicated the reaction to be both stereoselective for formation of 2,5-*cis*-THFs and



Scheme 8. Oxidative cyclization to form amino-THFs **46**–**49**.

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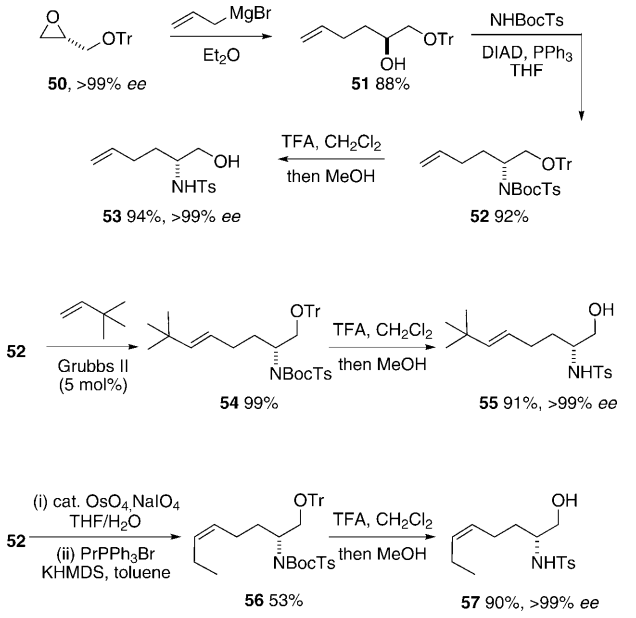
stereospecific with respect to addition across the alkene moiety.[17] The enantiomeric excess of THF **49** was determined by conversion into the Mosher's ester derivative and comparing the ^{19}F NMR spectra with those for the derivative of racemic material.[12] However, it was evident that carbamate-protected amino alcohol **40** cyclized much more slowly, and in slightly lower yield, than its sulfonamide analogue **39**. Moreover, a carbamate-protected nitrogen atom was consisitently shown to be a worse ligand for osmium than a sulfonamide-protected nitrogen atom throughout these studies (see below).

Pyrrolidine Formation Using Oxidative Cyclization

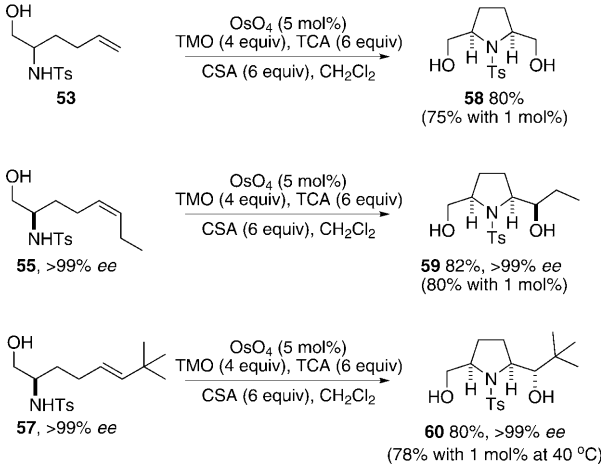
With an effective protocol in hand for the formation of THFs and amino-THFs, attention was turned to the construction of pyrrolidines by osmium-catalyzed oxidative cyclization from structurally-related amino alcohols to those shown above. The synthesis of the pyrrolidine scaffold in a concise, stereodefined manner has remained a challenging task in organic chemistry.[18] However, a novel nitrogen cyclization procedure would allow facile access to this structural moiety commonly found in many natural products.[19] Accordingly, amino alcohols **53**, **55**, and **57** were readily prepared from enantiopure glycidol utilizing cross-metathesis and Wittig methodology (Scheme 9).[12] Thus, allyl Grignard addition to commercially available trityl glycidol **50** and subsequent Mitsunobu reaction provided protected amino alcohol **52**, which was elaborated into amino alcohols **53**, **55**, and **57** as shown. The *trans* and *cis* geometries of **55** and **57** were assigned from the olefinic coupling constants of 15.7 and 9.8 Hz, respectively. The enantiomeric excesses of amino alcohols **55** and **57** were determined by conversion into the



Scheme 9. Synthesis of amino alcohols **53**, **55**, and **57**. Tr = trityl; Boc = *tert*-butoxycarbonyl; DIAD = diisopropyl azodicarboxylate; KHMDS = potassium bis(trimethylsilyl)amide.

Mosher's ester derivatives and by comparing the ^{19}F NMR spectra with those for the derivatives of racemic material.[12]

Subjection of compounds **53**, **55**, and **57** to catalytic osmium tetroxide in acidic dichloromethane furnished the corresponding pyrrolidines **58**, **59**, and **60** in high yields (Scheme 10). The use of camphorsulfonic acid (CSA) in dichloromethane gave the pyrrolidine products in higher yields than the TFA/acetone/water mixture that had proven optimal for diol cyclization.

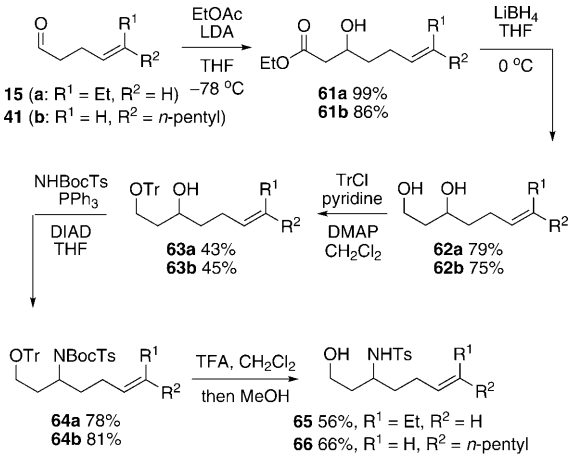


Scheme 10. Oxidative cyclization to form pyrrolidines **58**–**60**. CSA = (±)-camphorsulfonic acid.

Oxidative cyclization was also attempted with only one mole percent of osmium catalyst. Pleasingly, pyrrolidines **58** and **59** were formed in 75% and 80% yield, respectively. Amino alcohol **57** was considerably slower to cyclize than the others owing to the steric bulk of the *trans tert*-butyl-substituted olefin, but it proved possible to achieve a viable reaction with one mole percent of catalyst by performing the reaction at 40 °C. The relative product stereochemistries were determined by X-ray crystal structure analyses of **58**, **59**, and **60** and the enantiomeric excess of **59** and **60** by formation of the Mosher's ester derivatives. The X-ray crystal structures again confirmed that the reaction was stereoselective for formation of 2,5-*cis* heterocycles and stereospecific with respect to *syn* addition across the alkene. Thus, this new nitrogen cyclization reaction displayed the same stereochemical preferences as the parent THF-forming reactions, which was taken as good evidence that a similar mechanism was in operation. However, pyrrolidine formation was limited to the use of sulfonamide protecting groups, since the cyclization of the Cbz analogue of amino alcohol **53** (not shown) failed under a range of reaction conditions utilizing catalytic osmium (in agreement with the general observation that a sulfonamide-protected nitrogen atom was a better ligand for osmium than a carbamate-protected nitrogen atom).

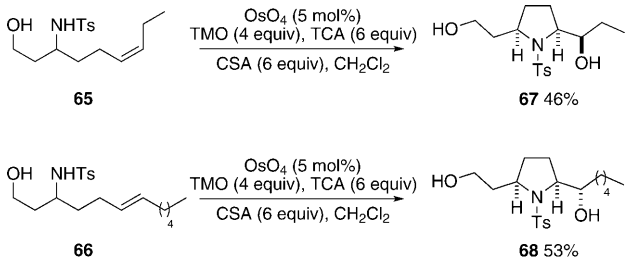
Next, 1,3-amino alcohols **65** and **66** were synthesized from the commercially available aldehydes **15** and **41** to examine

the effects of different initiator functionalities upon the oxidative cyclization reaction. Hence, aldolization, lithium borohydride ester reduction, selective protection of the primary hydroxyl group as the corresponding trityl ether, Mitsunobu reaction, and subsequent deprotection of both acid-labile protecting groups furnished the amino alcohols **65** and **66** (Scheme 11).



Scheme 11. Synthesis of 1,3-amino alcohols **65** and **66**.

Compounds **65** and **66** were then subjected to the oxidative reaction conditions that had proven optimal for the cyclization of 1,2-amino alcohols, to form pyrrolidines **67** and **68** as single diastereoisomers by ^{13}C NMR (Scheme 12).

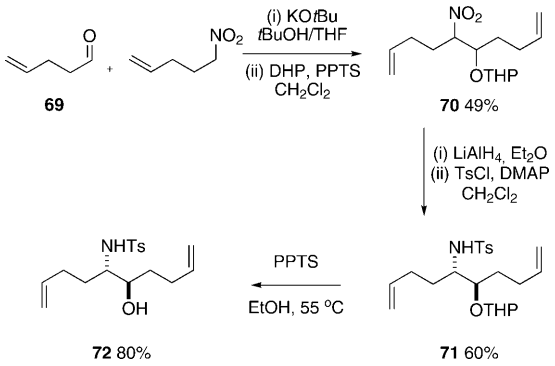


Scheme 12. Oxidative cyclization of 1,3-amino alcohol initiators **65** and **66**.

However, the times taken for the reactions to reach full conversion were longer and the yields poorer than for the corresponding 1,2-amino alcohols, precluding the use of lower catalyst loadings. Presumably, the 1,3-amino alcohols were again poorer ligands for the osmium metal, resulting in lower concentrations of the "loaded" 1,3-amino alcohol osmate ester cyclization precursors and therefore slower overall reaction rates. The relative stereochemistry of **67** was confirmed by X-ray crystal structure analysis;[17] given this result and the substantial precedent from the osmium-mediated oxidative cyclization reactions we have studied, we make the assumption that addition across the alkene moiety for **66** was also *syn*.

Mechanistic Investigations

Having observed that pyrrolidine formation was optimal with CSA in dichloromethane, while THF formation required the use of TFA in aqueous acetone, we were intrigued as to the relative rates of formation of the two types of heterocycle and whether it would be possible to form a pyrrolidine selectively over a THF (or vice versa) when a choice existed. To this end, competition substrate **72** was prepared in five steps from commercially available 4-pentenal (**69**) in 24% overall yield.[12] Thus, Henry reaction, alcohol protection, nitro reduction, and amine protection followed by alcohol deprotection provided amino alcohol **72** as a single diastereoisomer (Scheme 13). Intriguingly, the

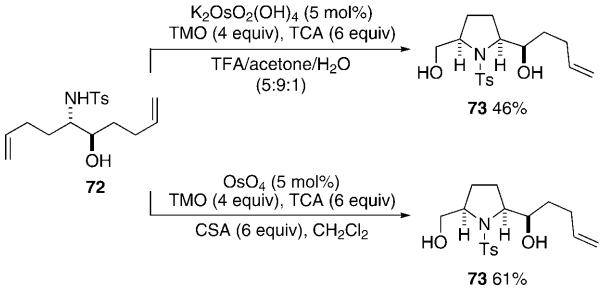


Scheme 13. Preparation of competition substrate amino alcohol **72**.

Henry reaction of **69** was essentially unselective, furnishing a 1.6:1 diastereomeric mixture. However, when this mixture was reduced with lithium aluminum hydride, a single diastereomer was formed (after tosylation and alcohol deprotection), suggesting deprotonation α to the nitrogen atom had occurred during the reaction, with subsequent selective reduction.

Oxidative cyclization of **72** utilizing TFA in aqueous acetone and CSA in dichloromethane furnished pyrrolidine **73** in 46% and 61% yields, respectively (Scheme 14). The structure of pyrrolidine **73** was confirmed by X-ray crystal structure analysis.

Interestingly, no THF formation was observed when either set of reaction conditions was applied to **72**. This ex-



Scheme 14. Oxidative cyclization of competition amino alcohol **72**.

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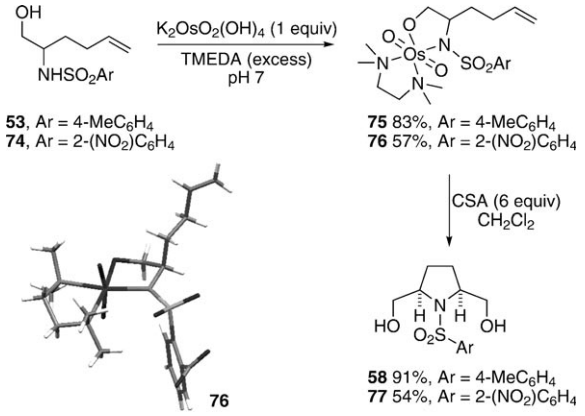
periment exemplified the overriding preference for the formation of nitrogen over oxygen heterocycles, providing further evidence for the enhanced activity of an Os–N unit over an Os–O bond when a choice exists, as previously found for both aminohydroxylation and diamination.[20] To investigate why this should be the case for the oxidative cyclization reaction, we developed a stoichiometric model (Scheme 15). Hence, treatment of amino alcohols **53** and **74** with stoichiometric osmium(VI) and TMEDA at pH 7 gave the stable azaglycolate osmate esters **75** and **76**.[21]



Scheme 15. Mechanistic probe for oxidative cyclization. TMEDA = *N,N,N′,N′*-tetramethylethylenediamine.

Gratifyingly, when compounds **75** and **76** were exposed to acidic dichloromethane, efficient cyclization to the corresponding pyrrolidines **58** and **77** occurred. The structure of azaglycolate osmate ester **76** was confirmed by X-ray crystal analysis, which revealed that the nitrogen atom bound to osmium was planar rather than pyramidal. This observation suggests significant double bond character between the nitrogen and osmium atoms. We suggest that the lesser electronegativity of nitrogen over oxygen allows for better Os–N π overlap than for Os–O, leading to greater participation of the Os–N unit in a pericyclic cyclization process. This rationale would help to explain why there is a greater propensity for cyclization of an Os–N unit over an Os–O unit.

Moreover, the sp^3 nature of a sulfonamide-protected nitrogen atom compared to the sp^2 nature of a carbamate-protected nitrogen atom suggests that the Os–N interaction (within an azaglycolate osmate ester) will be weaker for a carbamate-protected nitrogen atom (which will lose delocalization upon binding to osmium) than a sulfonamide-protected nitrogen atom (which will not). This effect was evident from the slower cyclization of carbamate **40** over sulfonamide **39** in the formation of amino-THFs **47** and **46**, respectively (see Scheme 8 above). Also, the failure of carbamate-protected amino alcohols to cyclize to the corresponding pyrrolidines was in stark contrast to the successful cyclization of sulfonamide-protected amino alcohols (see above).

Role of Acid in Oxidative Cyclization

Interestingly, when the azaglycolate osmate ester **75** was exposed to basic or neutral conditions, no cyclization was observed. However, treatment with acid furnished the corresponding pyrrolidine **58** in 91% yield. We believe that protonation of an Os=O unit in the intermediate osmate ester allows the bound osmium species to participate in a pericyclic process with the pendant alkene, facilitating cyclization. Protonation would be expected to lower the energy of the orbitals around Os, thus increasing the interaction with the HOMO of a relatively electron-rich alkene.[22]

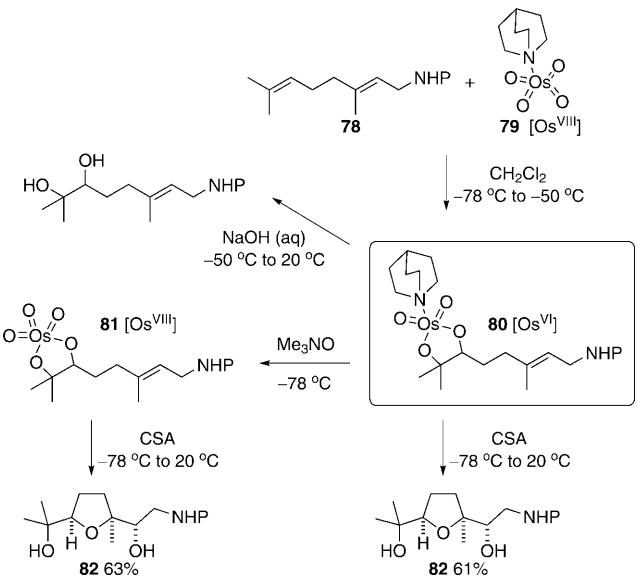
Osmium Oxidation State Considerations

The condensation of osmium(VI) with amino alcohols **53** and **74** (and subsequent cyclization) revealed that osmium(VI) was capable of mediating the oxidative cyclization reaction. The presence of osmium(VIII) was considered detrimental to yields and reaction times, since substrate dihydroxylation could occur instead of cyclization (see above). Hence, the role of the sacrificial alkene in the catalytic protocol is to be preferentially dihydroxylated by the excess osmium(VIII) to give a greater concentration of osmium(VI) in the reaction mixture. Therefore, the mechanism shown previously in Figure 1 must be treated as an oversimplification, since it is likely that a dihydroxylated molecule of TCA remains bound to the osmium catalyst throughout the catalytic cycle, exerting an effect similar to the "citrate effect" noted by Sharpless.[10] This osmium species can dihydroxylate other molecules of TCA upon oxidation to osmium(VIII), then suffer ligand exchange with a substrate molecule before undergoing an acid-mediated oxidative cyclization reaction across the pendant alkene.

Stoichiometric Probe of Osmium Oxidation States

To determine how the oxidation state of osmium affected the propensity of an osmate ester to undergo cyclization, we performed some stoichiometric studies on geranyl trichloroacetamide **78** (Scheme 16). These experiments were conducted using a system originally developed by Sharpless and co-workers to examine the effect of the second catalytic cycle in the asymmetric dihydroxylation reaction.[4]

Thus, addition of osmium tetroxide to quinuclidine in dichloromethane at −78 °C furnished the orange osmium(VIII) complex **79**. Subsequent addition of diene **78** and warming to −50 °C resulted in the formation of the green osmium(VI) ester **80**.[23] Exposure of this osmate ester to basic conditions only liberated the corresponding diol. However, acidification with CSA gave the THF **82** in 61% yield (whose structure was proven by conversion to the corresponding *para*-nitrobenzoyl derivative and subsequent X-ray crystal structure analysis), providing further evidence that osmium(VI) facilitates oxidative cyclization. Interestingly, treatment of osmate ester **80** with TMO gave the red osmate ester **81**[21] (not characterized), which also furnished



Scheme 16. Stoichiometric investigations to determine whether osmium oxidation state affects the propensity for oxidative cyclization (osmium oxidation states are shown in parentheses). P = trichloroacetamide.

THF **82** upon acidification with TMO. This experiment reveals that in the right setting osmium(VIII) is also capable of promoting acid-mediated oxidative cyclization reactions.

Proposed Catalytic Cycle

Although the exact nature of the osmium oxidation state during the catalytic reaction is unclear, the following conclusions can be drawn regarding a simplified osmium(VI)–osmium(IV) cycle: 1) osmium(VI) chelates efficiently to the substrate (see Scheme 15 above); 2) the subsequent osmium(VI) ester **83** suffers an acid-mediated oxidative cyclization reaction via transition structure **84** (Figure 2); 3) the resultant weakly bound osmium(IV) ester is hydrolyzed to give the product heterocycle and osmium(IV), which is reoxidized.

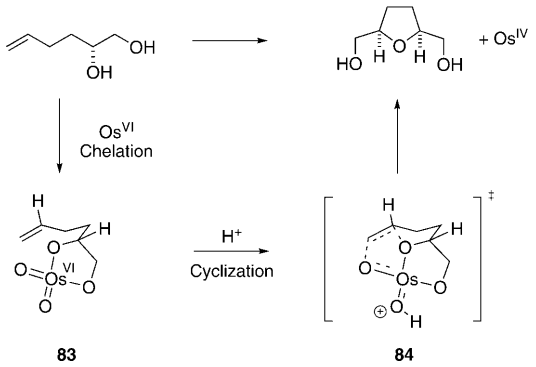


Figure 2. Simplified oxidative cyclization catalytic cycle for an osmium(VI)–osmium(IV)-mediated process (a diol has been arbitrarily chosen as the cyclization substrate and the dihydroxylated TCA ligand that is presumably bound to osmium has been omitted for clarity).

In addition to the simplified catalytic cycle shown in Figure 2, osmium(VIII) is present in the reaction mixture. We have no evidence to suggest that a substrate molecule (e.g., a diol or amino alcohol) can condense with osmium(VIII), since dihydroxylation of the starting material appears to be a more favorable process.[12] Hence, this side-reaction is tempered by the presence of TCA, which provides a higher concentration of osmium(VI), promoting oxidative cyclization over dihydroxylation. In addition, it is quite possible that the chelated osmium(VI) osmate ester could undergo oxidation to the corresponding chelated osmium(VIII) species, which could also cyclize to give the product heterocycle (see Scheme 16 above).[4] This would liberate osmium(VI) to the reaction mixture, available for further catalytic reactions. Of course, a bound osmium(VIII) species also has the potential to dihydroxylate other substrates and TCA molecules instead of undergoing cyclization. Thus, the proposed catalytic cycle in Figure 2 should be viewed as a simplified platform upon which several other catalytic processes operate, many with the same net result.

Conclusions

A powerful method for the construction of five-membered heterocycles has been developed using the catalytic osmium-mediated oxidative cyclization reaction. Judicious choice of chelating functionalities in the starting material gave rise to THF and pyrrolidine products in moderate to high yields, with near total selectivity for the formation of 2,5-*cis* heterocycles. 1,2-Diols, 1,2-amino alcohols, 1,2-hydroxy amides, and 1,3-diols were shown to cyclize to the corresponding THFs, while pyrrolidine formation was observed upon cyclization of 1,2- and 1,3-amino alcohols. Furthermore, enantiopure starting materials were shown to cyclize efficiently, allowing access to enantiopure heterocycles. Additionally, several mechanistic insights were revealed through competition experiments and stoichiometric studies. Thus, a mechanistic rationale was developed and the scope and limitations of this methodology were explored. The application of this synthetic tool to the construction of complex natural products bearing THF and pyrrolidine units is currently underway in our laboratories and will be reported in due course.

Experimental Section

General: Tetrahydrofuran and dichloromethane were purified prior to use by filtration through two activated alumina columns (activated basic aluminum oxide, Brockmann I, standard grade, ca. 150 mesh, 58 Å). Reagents obtained from Acros, Aldrich, Avocado, Fluka, and Lancaster fine chemicals suppliers were used directly. Flash column chromatography was carried out using silica gel 60 (0.040–0.063 mm; Merck) using head pressure by means of head bellows. Thin layer chromatography was performed on commercially available precoated aluminum-backed plates (0.25 mm silica gel with fluorescent indicator UV254). Visualization was achieved by either the quenching of UV fluorescence, $KMnO_4$, or vanillin stain. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE

AV400 (400 MHz and 100.6 MHz), Bruker DPX400 (400 MHz and 100.6 MHz), or a Bruker AVANCE AV500 (500 MHz and 125.7 MHz) spectrometer. Signal positions were recorded in δ (ppm) with the abbreviations s, d, t, q, qu, br, app, and m denoting singlet, doublet, triplet, quartet, quintet, broad, apparent, and multiplet, respectively. All NMR chemical shifts were referenced to residual solvent peaks or to $SiMe_4$ as an internal standard. All coupling constants, *J*, are quoted in Hz. IR spectra were recorded on a Bruker Tensor 27 FTIR spectrometer. Spectra were analyzed either as thin films between NaCl plates, KBr disks, or in a chloroform solution cell. Mass spectra (*m*/*z*) and HRMS were recorded under the conditions of electrospray (ESI), chemical (CI), and field (FI) ionization. Melting points were obtained using a Leica VMTG heated-stage microscope and are uncorrected. "Petrol" refers to the fraction of petroleum ether boiling in the range 40–60 °C unless otherwise stated and "ether" refers to diethyl ether.

General pocedure A: Aldol reaction: *n*Butyllithium (1.6 M in hexanes, 3.1 equiv) was added dropwise to a solution of diisopropylamine (3.1 equiv) in THF (7.7 mL per mmol substrate) and stirred for 20 min at 0 °C before cooling to −78 °C. Freshly distilled ethyl acetate (3.0 equiv) was added dropwise and the mixture was stirred for a further 20 min. Aldehyde (1.0 equiv) was added dropwise and the mixture stirred at −78 °C for 2 h. The reaction was quenched by dropwise addition of saturated aqueous NH_4Cl (5 mL) and extracted with ether (3×25 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, and concentrated to yield the crude product, which was purified as indicated.

General procedure B: TFA-mediated oxidative cyclization: The cyclization substrate (1.0 equiv) and trimethylamine *N*-oxide dihydrate (5.0 equiv) were dissolved in a 9:1 mixture of acetone/water (20 mL per mmol substrate) and the solution cooled to 0 °C. *trans*-Cinnamic acid (5.0 equiv) and trifluoroacetic acid (10 mL per mmol substrate) were added, followed immediately by potassium osmate dihydrate (5 mol %). The reaction was warmed to room temperature and stirred for 16 h, then quenched by addition of solid sodium sulfite (0.5 equiv) and stirred for 30 min. The resulting mixture was cooled to 0 C and neutralized by careful addition of aqueous NaOH (40 % by weight, saturated with NaCl). Ethyl acetate (20 mL) was added and the layers separated. The organic layer was washed with water (20 mL) and the combined aqueous phases extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give the crude product, which was purified as indicated.

General procedure C: CSA-mediated oxidative cyclization: The cyclization substrate (1.0 equiv), (±)-camphorsulfonic acid (6.0 equiv), and trimethylamine *N*-oxide dihydrate (4.0 equiv) were dissolved in CH_2Cl_2 (25 mL per mmol substrate). *trans*-Cinnamic acid (5.0 equiv) was added, followed immediately by osmium tetroxide (5 mol %), and the resulting solution was stirred at room temperature for 16 h. In the case of starting material remaining after this time, a further portion of (±)-camphorsulfonic acid (6.0 equiv) was added and the reaction monitored by TLC until complete. The reaction was quenched by addition of solid sodium sulfite (0.5 equiv) and stirred for 30 min. The reaction mixture was washed with aqueous NaOH (2 M, 25 mL) and extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated to give the crude product, which was purified as indicated.

(±)-(*E*)-Ethyl 8-(benzyloxy)-3-hydroxy-6-methyloct-6-enoate (**8**): (*E*)-6-(Benzyloxy)-4-methylhex-4-enal (**7**; 0.75 g, 3.4 mmol) was subjected to general procedure A. Purification by flash column chromatography (SiO_2, 1:2 ether:petrol) gave hydroxy-ester **8** (0.92 g, 3.0 mmol, 88 %) as an oil; IR (thin film): $\tilde{\nu}_{max}$ = 3452, 2978, 1725, 1276 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz): δ_H = 7.35–7.27 (5H, m), 5.44 (1H, t, *J* 6.8), 4.51 (2H, s), 4.18 (2H, q, *J* 7.2), 4.03 (2H, d, *J* 6.8), 4.01–3.97 (1H, m), 2.97 (1H, br s), 2.51 (1H, dd, *J* 16.4 and 3.4), 2.43 (1H, dd, *J* 16.4 and 8.7), 2.26–2.19 (1H, m), 2.15–2.05 (1H, m), 1.66 (3H, s), 1.62–1.53 (2H, m), 1.28 ppm (3H, t, *J* 7.2); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 172.9, 139.8, 138.5, 128.3, 127.8, 127.5, 121.3, 72.1, 67.7, 66.5, 60.7, 41.3, 35.4, 34.4, 16.5, 14.2 ppm; MS *m*/*z* (ESI^+) 329 (100 %, $M+Na^+$); HRMS (ESI^+) calcd for $C_{18}H_{26}O_4Na$ [$M+Na^+$]: 329.1723; found: 329.1713 (+3.2 ppm).

(±)-(*E*)-8-(Benzyloxy)-6-methyloct-6-ene-1,3-diol (**9**): Lithium borohydride (0.21 g, 9.7 mmol) was added to a stirred solution of hydroxy-ester **8** (2.0 g, 6.4 mmol) in THF (50 mL) at 0 °C, then warmed to room temperature and stirred for 4 h. The reaction was quenched with water (50 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (SiO_2, 1:2 acetone/petrol) gave diol **9** (1.6 g, 6.0 mmol, 92 %) as an oil; IR (thin film): $\tilde{\nu}_{max}$ = 3408, 2936, 1719, 1452, 1277, 1068 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.36–7.35 (4H, m), 7.31–7.27 (1H, m), 5.44 (1H, t, *J* 6.7), 4.51 (2H, s), 4.03 (2H, d, *J* 6.7), 3.89–3.76 (3H, m), 2.73 (2H, br s), 2.22–2.06 (2H, m), 1.71–1.58 ppm (7H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 140.3, 138.4, 128.4, 127.8, 127.6, 121.1, 72.2, 71.8, 66.5, 61.6, 38.3, 35.6, 35.5, 16.5 ppm; MS *m*/*z* (ESI^+) 287 (100 %, $M+Na^+$); HRMS (ESI^+) calcd for $C_{16}H_{24}O_3Na$ [$M+Na^+$]: 287.1618; found: 287.1618 (+0.1 ppm).

(±)-*(S)*-2-(Benzyloxy)-1-((2*S*,5*R*)-5-(2-hydroxyethyl)-2-methyltetrahydrofuran-2-yl)ethanol (**18**): The diol **9** (80 mg, 0.30 mmol) was subjected to general procedure B. Purification by flash column chromatography (florisil, eluting with 4:1 petrol/acetone) gave the THF **18** (69 mg, 0.25 mmol, 82 %) as an oil; IR (thin film): $\tilde{\nu}_{max}$ = 3417, 2930, 1680, 1453, 1260, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.35–7.27 (5H, m), 4.56 (2H, dd, *J* 18.9, 11.8), 4.23–4.16 (1H, m), 3.77 (2H, t, *J* 5.5), 3.67 (1H, dd, *J* 7.4, 3.4), 3.59 (1H, dd, *J* 9.7, 3.4), 3.49 (1H, dd, *J* 9.7, 7.4), 2.81 (2H, br s), 2.17–1.99 (2H, m), 1.78–1.74 (2H, m), 1.69–1.56 (2H, m), 1.17 ppm (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 137.9, 128.4, 127.8, 127.7, 84.4, 78.5, 75.5, 73.5, 71.2, 61.1, 37.5, 34.4, 31.9, 22.7 ppm; MS *m*/*z* (ESI^+) 303 (100 %, $M+Na^+$); HRMS (ESI^+) calcd for $C_{16}H_{24}O_4Na$ [$M+Na^+$]: 303.1567; found: 303.1567 (+0.0 ppm).

(±)-(*E*)-9-(Benzyloxy)-2,7-dimethylnon-7-ene-2,4-diol (**10**): Methylmagnesium chloride (3.0 M solution in THF, 1.9 mL, 5.7 mmol) was added dropwise over 2 min to a solution of hydroxy-ester **8** (350 mg, 1.1 mmol) in THF at −78 °C under an atmosphere of argon. The mixture was warmed to room temperature and stirred for 16 h. Saturated aqueous NH_4Cl (5 mL) was added followed by ethyl acetate (10 mL). The separated aqueous layer was extracted with ethyl acetate (2×20 mL) and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, and then concentrated to give the crude product. Purification by flash column chromatography (SiO_2, 1:4 acetone/petrol) to give the tertiary alcohol **10** (240 mg, 0.83 mmol, 73 %) as a viscous oil; IR (thin film): $\tilde{\nu}_{max}$ = 3420, 2971, 1718, 1452, 1377, 1275, 1118 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.35–7.28 (5H, m), 5.44 (1H, t, *J* 6.8), 4.51 (2H, s), 4.01 (2H, d, *J* 6.8), 4.03–3.97 (1H, m), 3.51 (1H, br s), 3.05 (1H, br s), 2.20–2.05 (2H, m), 1.66 (3H, s), 1.68–1.49 (4H, m), 1.30 (3H, s), 1.26 ppm (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 140.4, 138.4, 128.4, 127.8, 127.6, 121.0, 72.1, 71.7, 69.5, 66.5, 47.7, 36.1, 35.5, 32.1, 27.7, 16.5 ppm; MS *m*/*z* (ESI^+) 315 (100 %, $M+Na^+$); HRMS (ESI^+) calcd for $C_{18}H_{28}O_3Na$ [$M+Na^+$]: 315.1936; found: 315.1930 (−0.2 ppm).

(±)-1-((2*R*,5*S*)-5-((*S*)-2-(Benzyloxy)-1-hydroxyethyl)-5-methyltetrahydrofuran-2-yl)-2-methylpropan-2-ol (**19**): The tertiary alcohol **10** (105 mg, 0.36 mmol) was subjected to general procedure B. Purification by flash column chromatography (florisil, eluting with 3:1 petrol/acetone) gave the THF **19** (74 mg, 0.24 mmol, 67 %) as an oil; IR (thin film): $\tilde{\nu}_{max}$ = 3426, 2970, 1719, 1275, 1095 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.37–7.28 (5H, m), 4.55 (2H, s), 4.36–4.29 (1H, m), 3.65 (1H, dd, *J* 6.9, 3.3), 3.60 (1H, dd, *J* 9.7, 3.3), 3.49 (1H, dd, *J* 9.7, 6.9), 2.20–2.13 (1H, m), 2.09–2.02 (1H, m), 1.72 (1H, dd, 13.3, 10.6), 1.62–1.53 (3H, m), 1.28 (3H, s) 1.22 (3H, s), 1.18 ppm (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C = 138.0, 128.5, 127.8, 127.5, 85.0, 76.5, 75.2, 73.5, 71.2, 70.5, 47.6, 33.9, 32.6, 30.8, 28.2, 23.2 ppm; MS *m*/*z* (ESI^+) 331 (100 %, $M+Na^+$); HRMS (ESI^+) calcd for $C_{18}H_{28}O_4Na$ [$M+Na^+$]: 331.1880; found: 331.1876 (+1.0 ppm).

(±)-(*Z*)-Ethyl 8-(benzyloxy)-3-hydroxy-6-methyloct-6-enoate (**13**): (*Z*)-6-(Benzyloxy)-4-methylhex-4-enal **12** (0.730 g, 3.3 mmol) was subjected to general procedure A. Purification by flash column chromatography (SiO_2, 1:2 ether/petrol) gave hydroxy-ester **13** (0.97 g, 3.2 mmol, 95 %) as an oil; IR (thin film): $\tilde{\nu}_{max}$ = 3457, 2980, 1724, 1452, 1375, 1276, 1027 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 7.35–7.34 (4H, m), 7.30–7.27 (1H, m), 5.48 (1H, t, *J* 7.0), 4.52 (2H, s), 4.16 (2H, q, *J* 7.1), 4.05 (1H, dd, *J* 11.0,

7.3), 3.98–3.94 (2H, m), 3.36 (1H, brs), 2.44–2.42 (2H, m), 2.33–2.26 (1H, m), 2.15–2.09 (1H, m), 1.76 (3H, s), 1.59–1.53 (2H, m), 1.27 ppm (3H, t, J 7.1); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C=172.7, 141.0, 138.2, 128.4, 127.9, 127.6, 122.0, 72.3, 67.0, 65.9, 60.6, 41.5, 34.4, 27.8, 23.2, 14.2 ppm; MS m/z (ESI$^+$) 329, (100%, M+Na$^+$); HRMS (ESI$^+$) calcd for $C_{18}H_{26}O_4Na$ [M+Na$^+$]: 329.1723; found: 329.1726 (−0.9 ppm).

(±)-(*Z*)-8-(Benzyloxy)-6-methyloct-6-ene-1,3-diol (**14**): Lithium borohydride (0.093 g, 4.3 mmol) was added to a stirred solution of hydroxy-ester **13** (0.87 g, 2.9 mmol) in THF (20 mL) at 0°C, then warmed to room temperature and stirred for 4 h. The reaction was quenched with water (20 mL) and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (SiO_2, 1:2 acetone/petrol) gave diol **14** (0.54 g, 2.1 mmol, 72%) as a viscous oil; IR (thin film/cm^{-1}): $\tilde{\nu}_{max}$=3408, 2936, 1719, 1452, 1277, 1068; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H=7.36–7.27 (5H, m), 5.54 (1H, t, J 7.3), 4.53 (2H, s), 4.09 (1H, dd, J 10.9, 7.7), 3.89 (1H, dd, J 10.9, 7.0), 3.77–3.71 (3H, m), 2.92 (2H, brs), 2.40 (1H, dt, J 13.2, 8.1), 2.05 (1H, dt, J 13.2, 6.0), 1.75 (3H, s), 1.67–1.56 ppm (4H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C=142.6, 137.7, 128.4, 128.1, 127.9, 121.4, 72.6, 70.6, 65.6, 61.9, 38.3, 35.0, 27.6, 23.0 ppm; MS m/z (ESI$^+$) 287 (100%, M+Na$^+$); HRMS (ESI$^+$) calcd for $C_{16}H_{24}O_3Na$ [M+Na$^+$]: 287.1618; found: 287.1618 (+0.0 ppm).

(±)-(*R*)-2-(Benzyloxy)-1-((2*S*,5*R*)-5-(2-hydroxyethyl)-2-methyltetrahydrofuran-2-yl)ethanol (**20**): Diol **14** (160 mg, 0.61 mmol) was subjected to general procedure B. Purification by flash column chromatography (florisil, eluting with 4:1 petrol/acetone) gave the THF **20** (140 mg, 0.49 mmol, 80%) as an oil; IR (thin film): $\tilde{\nu}_{max}$=3410, 2935, 1718, 1452, 1374, 1276, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H=7.38–7.29 (5H, m), 4.58 (2H, s), 4.23–4.06 (3H, m), 3.73 (1H, dd, J 7.7, 3.1), 3.66 (1H, dd, J 9.7, 7.7), 3.49 (1H, dd, J 9.7, 7.7), 2.21–2.08 (2H, m), 1.88–1.76 (2H, m), 1.64–1.54 (2H, m), 1.28 ppm (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C=138.0, 128.4, 127.7, 127.7, 84.2, 77.2, 75.4, 73.4, 71.1, 62.0, 34.9, 33.0, 31.6, 22.5 ppm; MS m/z (ESI$^+$) 303 (100%, M+Na$^+$); HRMS (ESI$^+$) calcd for $C_{16}H_{24}O_4Na$ [M+Na$^+$]: 303.1567; found: 303.1568 (−0.6 ppm).

(±)-(*Z*)-Ethyl 3-hydroxynon-6-enoate (**16**): *cis*-4-Heptenal **15** (0.580 mL, 4.5 mmol) was subjected to general procedure A. Purification by flash column chromatography (SiO_2, 1:3 ether/petrol) furnished hydroxy-ester **16** (0.89 g, 4.5 mmol, 100%) as an oil; IR (thin film): $\tilde{\nu}_{max}$=3346, 1730, 1648, 1373, 1301, 1189 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H=5.43–5.37 (1H, m), 5.35–5.28 (1H, m), 4.17 (2H, q, J 7.2), 4.05–3.97 (1H, m), 3.01 (1H, brs), 2.50 (1H, dd, J 16.4, 3.4), 2.41 (1H, dd, J 16.4, 8.9), 2.21–2.11 (2H, m), 2.05 (2H, qu, J 7.5), 1.63–1.54 (1H, m), 1.51–1.42 (1H, m), 1.27 (3H, t, J 7.2), 0.95 ppm (3H, t, J 7.5); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C=173.0, 132.5, 128.1, 67.5, 60.7, 41.3, 36.4, 23.2, 20.5, 14.3, 14.2 ppm; MS m/z (ESI$^+$) 223 (100%, M+Na$^+$); HRMS (ESI$^+$) calcd for $C_{11}H_{20}O_3Na$ [M+Na$^+$]: 223.1305; found: 223.1307 (−0.9 ppm).

(±)-(Z)-Non-6-ene-1,3-diol (**17**): Lithium borohydride (0.760 g, 35.0 mmol) was added to a stirred solution of hydroxy-ester **16** (1.7 g, 8.7 mmol) in THF (110 mL) at 0°C, warmed to room temperature, and stirred for 16 h. The reaction was quenched with water (50 mL) and extracted with ether (3×30 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. Purification by flash column chromatography (SiO_2, eluting with 1:4 acetone/petrol) gave diol **17** (1.1 g, 6.9 mmol, 79%) as an oil; IR (thin film): $\tilde{\nu}_{max}$=3333, 1654, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H=5.45–5.31 (2H, m), 3.92–3.80 (3H, m), 2.58 (2H, s), 2.23–2.09 (2H, m), 2.10–2.03 (2H, m), 1.77–1.65 (2H, m), 1.62–1.48 (2H, m), 0.97 ppm (3H, t, J 7.5); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C=132.5, 128.3, 72.1, 61.8, 38.3, 37.6, 23.4, 20.5, 14.3 ppm; MS m/z (ESI$^+$) 181 (100%, M+Na$^+$); HRMS (ESI$^+$) calcd for $C_9H_{18}O_2Na$ [M+Na]: 181.1199; found: 181.1203 (−2.4 ppm).

(±)-(*R*)-1-((2*S*,5*R*)-5-(2-Hydroxyethyl)tetrahydrofuran-2-yl)propan-1-ol (**21**): Diol **17** (180 mg, 1.1 mmol) was subjected to general procedure B. Purification by flash column chromatography (florisil, eluting with 3:1 petrol/acetone) gave the THF **21** (130 mg, 0.75 mmol, 66%) as an oil; IR (thin film): $\tilde{\nu}_{max}$=3383, 2964, 1657, 1462, 1072 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H=4.09 (1H, qu, J 6.7), 3.88 (1H, dt, J 7.4, 3.4), 3.81 (2H, t, J 5.4), 3.72–3.68 (1H, m), 2.06–1.88 (2H, m), 1.82–1.75 (3H, m), 1.64–1.55 (1H, m), 1.48–1.40 (2H, m), 1.00 ppm (3H, t, J 7.4); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C=82.7, 79.4, 73.2, 61.6, 37.3, 31.6, 25.8, 23.8, 10.4 ppm; MS m/z (ESI$^+$) 197 (100%, M+Na$^+$); HRMS (ESI$^+$) calcd for $C_{19}H_{18}O_3Na$ [M+Na$^+$]: 197.1148; found: 197.1149 (−0.4 ppm).

(*S*)-4-Benzyl-3-((2*S*,3*R*,*E*)-8-(benzyloxy)-3-hydroxy-2,6-dimethyloct-6-enoyl)oxazolidin-2-one (**23**): Dibutylboryl trifluoromethanesulfonate (1.0 M solution in ether, 2.6 mL, 2.6 mmol) was added dropwise over 5 min to a solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one (0.50 g, 2.1 mmol) in CH_2Cl_2 (20 mL) at 0°C. Triethylamine (0.41 mL. 3.0 mmol) was then added dropwise over 5 min to give a light yellow solution which was cooled to −78°C. (*E*)-6-(Benzyloxy)-4-methylhex-4-enal (**7**, 0.70 g, 3.2 mmol) was added dropwise over 5 min. After 30 min the solution was warmed to 0°C and stirred at that temperature for 4 h. Phosphate buffer (pH 7, 3 mL) and methanol (5 mL) were then added followed by a mixture of aqueous hydrogen peroxide (30%, 3 mL) and methanol (5 mL) dropwise by syringe over 5 min. The mixture was stirred for 1 h and then concentrated. The mixture was extracted with ether (3×50 mL) and the combined organic extracts were washed sequentially with saturated aqueous sodium hydrogencarbonate (50 mL) and brine (50 mL), dried over $MgSO_4$, and then concentrated. The crude residue was purified by flash column chromatography (SiO_2, 1:9→1:4 acetone/petrol) to give the alcohol **23** (0.83 g, 1.8 mmol, 86%) as a viscous oil; $[\alpha]_D^{22}$=+40.0 (c=1.0 in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$=3480, 2937, 1779, 1699, 1453, 1384, 1212, 1110 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H=7.37–7.28 (8H, m), 7.21 (2H, d, J 7.1), 5.46 (1H, t, J 6.8), 4.72–4.66 (1H, m), 4.51 (2H, s), 4.23–4.16 (2H, m), 4.04 (2H, d, J 6.8), 3.97–3.93 (1H, m), 3.77 (1H, dq, J 6.9, 2.7), 3.25 (1H, dd, J 13.4, 3.3), 2.94 (1H, brs), 2.79 (1H, dd, J 13.4, 9.5), 2.30–2.22 (1H, m), 2.15–2.06 (1H, m), 1.74–1.65 (1H, m), 1.67 (3H, s), 1.60–1.52 (1H, m), 1.28 ppm (3H, d, J 6.9); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C=177.4, 153.0, 139.9, 138.5, 135.0, 129.4, 129.0, 128.4, 127.8, 127.6, 127.5, 121.3, 72.1, 71.0, 66.6, 66.2, 55.1, 42.2, 37.8, 35.9, 31.7, 16.5, 10.6 ppm; MS m/z (ESI$^+$) 474 (100%, M+Na$^+$); HRMS (ESI$^+$) calcd for $C_{27}H_{33}NO_5Na$ [M+Na$^+$]: 474.2251; found: 474.2254 (−0.8 ppm).

(2*R*,3*R*,*E*)-8-(Benzyloxy)-2,6-dimethyloct-6-ene-1,3-diol (**24**): Lithium borohydride (0.087 g, 4.0 mmol) was added to a stirred solution of alcohol **23** (1.2 g, 2.7 mmol) in THF (20 mL) containing water (1 mL) at 0°C, then warmed to room temperature and stirred for 16 h. The reaction was quenched with water (20 mL) and extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$, and concentrated. Purification by flash column chromatography (SiO_2, 1:6→1:3 acetone/petrol) gave diol **24** (0.52 g, 1.9 mmol, 71%) as a viscous oil; $[\alpha]_D^{22}$=+4.0 (c=1.0 in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$=3425, 2958, 1032 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H=7.35–7.27 (5H, m), 5.44 (1H, t, J 7.0), 4.51 (2H, s), 4.03 (2H, d, J 7.0), 3.79–3.78 (1H, m), 3.66 (2H, d, J 5.4), 2.82 (2H, m), 2.25–2.18 (1H, m), 2.11–2.05 (1H, m), 1.81–1.75 (1H, m), 1.66 (3H, s), 1.65–1.49 (2H, m), 0.89 ppm (3H, d, J 7.1); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C=140.4, 138.3, 128.4, 127.9, 127.6, 121.0, 73.9, 72.2, 66.9, 66.6, 39.2, 36.3, 31.7, 16.5, 10.3 ppm.

(*R*)-2-((2*R*,5*S*)-5-((*S*)-2-(Benzyloxy)-1-hydroxyethyl)-5-methyltetrahydrofuran-2-yl)propan-1-ol (**25**): Diol **24** (120 mg, 0.44 mmol) was subjected to general procedure B. Purification by flash column chromatography (florisil, eluting with 4:1 petrol/acetone) gave the THF **25** (105 mg, 0.36 mmol, 81%) as an oil; $[\alpha]_D^{22}$=+9.5 (c=1.0 in $CHCl_3$); IR (thin film): $\tilde{\nu}_{max}$=3428, 2967, 1715, 1454, 1372, 1095 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H=7.36–7.27 (5H, m), 4.58 (1H, d, J 11.8), 4.52 (1H, d, J 11.8), 4.11–4.06 (1H, m), 3.70–3.46 (5H, m), 2.79 (2H, brs), 2.11–1.98 (2H, m), 1.90–1.72 (2H, m), 1.65–1.58 (1H, m), 2.91 (3H, s), 0.87 ppm (3H, d, J 7.1); ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C=137.9, 128.5, 127.7, 127.7, 83.4, 81.6, 75.5, 73.5, 71.2, 65.5, 38.0, 34.9, 27.6, 22.1, 12.6 ppm; MS m/z (ESI$^+$) 317 (100%, M+Na$^+$), 295 (25%, MH$^+$); HRMS (ESI$^+$) calcd for $C_{17}H_{26}O_4Na$ [M+Na$^+$]: 317.1729; found: 317.1729 (+0.1 ppm).

(±)-(*R*)-1-((2*S*,5*R*)-5-(2-Hydroxyethyl)-1-tosylpyrrolidin-2-yl)propan-1-ol (**67**): Amino alcohol **65** (0.19 g, 0.61 mmol) was subjected to general procedure C. Flash column chromatography (SiO_2, 15:85 acetone/petrol) gave pyrrolidine **67** (0.091 g, 0.28 mmol, 46%) as needles; m.p. 86–87°C; IR (KBr disc): $\tilde{\nu}_{max}$=3416, 1598, 1494, 1449, 1340, 1158, 1091 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H=7.73 (2H, d, J 8.2), 7.35 (2H, d, J 8.2), 4.04–3.84 (4H, m), 3.52 (1H, ddd, J 9.8, 7.8, 2.4), 2.67 (2H, brs), 2.45

(3H, s), 1.98 (1H, tdd, *J* 12.8, 9.5, 6.7), 1.83 (1H, dddd, *J* 14.1, 10.9, 5.9, 3.0), 1.65–1.55 (2H, m), 1.45–1.36 (3H, m), 1.10 (1H, tt, *J* 12.6, 7.4), 1.03 ppm (3H, t, *J* 7.4); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 144.0, 133.9, 129.9, 127.7, 73.4, 66.7, 59.6, 59.4, 37.0, 30.1, 25.9, 23.2, 21.6, 10.8 ppm; MS *m*/*z* (ESI$^+$) 350 (60%, *M*+Na$^+$), 386 (80%, *M*+NH$_4^+$+MeCN), 677 (10%, 2M+Na$^+$), 713 (100%, 2M+NH$_4^+$+MeCN); HRMS (ESI$^+$) calcd for $C_{16}H_{25}NO_4SNa$ [*M*+Na$^+$]: 350.1397; found: 350.1396 (+0.3 ppm).

(±)-(*S*)-1-((2*S*,5*R*)-5-(2-Hydroxyethyl)-1-tosylpyrrolidin-2-yl)hexan-1-ol (**68**): Amino alcohol **66** (0.23 g, 0.65 mmol) was subjected to general procedure C. Flash column chromatography (SiO_2, eluting with 15:85 acetone/petrol) gave pyrrolidine **68** (0.13 g, 0.34 mmol, 53%) as an oil; IR (thin film): $\tilde{\nu}_{max}$ = 3426, 1598, 1494, 1454, 1338, 1158, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.74 (2H, d, *J* 8.1), 7.35 (2H, d, *J* 8.1), 4.13–4.07 (1H, m), 3.98 (1H, ddd, *J* 12.2, 9.8, 3.8), 3.75 (1H, dt, *J* 12.2, 3.8), 3.49 (1H, app. q, *J* 7.7), 3.41 (1H, td, *J* 8.5, 2.1), 2.45 (3H, s), 2.37 (2H, br s), 1.76–1.55 (5H, m), 1.50–1.21 (9H, m,), 0.90 ppm (3H, t, *J* 7.0); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 144.3, 134.0, 130.0, 127.7, 74.8, 66.6, 59.2, 58.9, 38.2, 34.0, 32.0, 30.1, 27.8, 25.1, 22.6, 21.6, 14.1 ppm; MS *m*/*z* (ESI$^+$) 392 (10%, *M*+Na$^+$), 428 (100%, *M*+NH$_4^+$+MeCN), 797 (35%, 2M+NH$_4^+$+MeCN); HRMS (ESI$^+$) calcd for $C_{19}H_{31}NO_4SNa$ [*M*+Na$^+$]: 392.1866; found: 392.1866 (+0.1 ppm).

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[1] For a review see: a) V. Piccialli, *Synthesis* **2008**, 2585–2607; manganese: b) E. Klein, W. Rojahn, *Tetrahedron* **1965**, *21*, 2353–2358; c) J. E. Baldwin, M. J. Crossley, E. M. M. Lehtonen, *J. Chem. Soc. Chem. Commun.* **1979**, 918–920; d) D. M. Walba, M. D. Wand, M. C. Wilkes, *J. Am. Chem. Soc.* **1979**, *101*, 4396–4397; e) R. C. D. Brown, J. F. Keily, *Angew. Chem.* **2001**, *113*, 4628–4630; *Angew. Chem. Int. Ed.* **2001**, *40*, 4496–4498; f) R. C. D. Brown, C. J. Bataille, R. M. Hughes, A. Kenney, T. J. Luker, *J. Org. Chem.* **2002**, *67*, 8079–8085; ruthenium: g) P. H. J. Carlsen, T. Katsuki, V. S. Martin, K. B. Sharpless, *J. Org. Chem.* **1981**, *46*, 3936–3938; h) L. Albarella, D. Musumeci, D. Sica, *Eur. J. Org. Chem.* **2001**, 997–1003; i) V. Piccialli, N. Cavallo, *Tetrahedron Lett.* **2001**, *42*, 4695–4699; j) S. Roth, S. Gohler, H. Cheng, C. B. W. Stark, *Eur. J. Org. Chem.* **2005**, 4109–4118; osmium: k) M. de Champdore, M. Lasalvia, V. Piccialli, *Tetrahedron Lett.* **1998**, *39*, 9781–9784.

[2] T. J. Donohoe, S. Butterworth, *Angew. Chem.* **2003**, *115*, 978–981; *Angew. Chem. Int. Ed.* **2003**, *42*, 948–951.

[3] a) R. M. Kennedy, S. Tang, *Tetrahedron Lett.* **1992**, *33*, 3729–3732; b) S. Tang, R. M. Kennedy, *Tetrahedron Lett.* **1992**, *33*, 5299–5302.

[4] J. S. M. Wai, I. Markó, J. M. Svendsen, M. G. Finn, E. N. Jacobsen, K. B. Sharpless, *J. Am. Chem. Soc.* **1989**, *111*, 1123–1125.

[5] a) T. J. Donohoe, S. Butterworth, *Angew. Chem.* **2005**, *117*, 4844–4846; *Angew. Chem. Int. Ed.* **2005**, *44*, 4766–4768; for a related chromium-mediated cyclization, see: b) D. M. Walba, G. S. Stoudt, *Tetrahedron Lett.* **1982**, *23*, 727–730.

[6] *cis*-Solamin: a) see reference [5a]; *cis*-sylvaticin: b) T. J. Donohoe, R. M. Harris, J. Burrows, J. Parker, *J. Am. Chem. Soc.* **2006**, *128*, 13704–13705.

[7] M. Z. Hoemann, Z. Michael, K. A. Agrios, J. Aube, *Tetrahedron* **1997**, *53*, 11087–11098.

[8] P. Grieco, Y. Musaki, D, Boxler, *J. Am. Chem. Soc.* **1975**, *97*, 1597–1599.

[9] R. D. Hancock, A. E. Martell, *Chem. Rev.* **1989**, *89*, 1875–1914.

[10] P. Dupau, R. Epple, A. A. Thomas, V. V. Fokin, K. B. Sharpless, *Adv. Synth. Catal.* **2002**, *344*, 421–433.

[11] a) V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 3563–3565; b) M. A. Andersson, R. Epple, V. V. Fokin, K. B. Sharpless, *Angew. Chem.* **2002**, *114*, 490–493; *Angew. Chem. Int. Ed.* **2002**, *41*, 472–475.

[12] T. J. Donohoe, G. H. Churchill, K. M. P. Wheelhouse (née Gosby), P. A. Glossop, *Angew. Chem.* **2006**, *118*, 8193–8196; *Angew. Chem. Int. Ed.* **2006**, *45*, 8025–8028.

[13] J. R. Gage, D. A. Evans, *Org. Synth. Coll. Vol. VIII*, **1993**, 339–443.

[14] Rhenium: a) see reference [3]; cobalt: b) S. Inoki, T. Mukaiyama, *Chem. Lett.* **1990**, 67–70.

[15] For reports on the oxidative cyclization of 1,6-dienes using ruthenium, see: a) V. Piccialli, *Tetrahedron Lett.* **2000**, *41*, 3731–3733; b) S. Roth, B. W. Stark, *Angew. Chem.* **2006**, *118*, 6364–6367; *Angew. Chem. Int. Ed.* **2006**, *45*, 6218–6221; manganese: c) R. L. Cecil; R. C. D. Brown, *Tetrahedron Lett.* **2004**, *45*, 7269–7271; R. C. D. Brown, *Tetrahedron Lett.* **2004**, *45*, 7269–7271.

[16] a) See reference [4]; b) K. Muñiz, I. Almodovar, J. Streuff, M. Nieger, *Adv. Synth. Catal.* **2006**, *348*, 1831–1835.

[17] Data were collected at low temperature using an Enraf–Nonius KCCD diffractometer [Z. Otwinowski, W. Minor, Processing of X-ray Diffraction Data Collected in Oscillation Mode, In *Methods Enzymol., Vol. 276* (Eds.: C. W. Carter, R. M. Sweet), Academic Press, **1997**]. The crystal structures were solved using SIR92 [A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435.] and refined using the CRYSTALS software suite [P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, *36*, 1487], as per the CIF. Crystallographic data (excluding structure factors) for compound **67** have been deposited with the Cambridge Crystallographic Data Centre (CCDC 730223) and copies of these data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

[18] For examples of pyrrolidine synthesis using catalysis, see: a) C. V. Galliford, M. A. Beenen, S. T. Nguyen, K. A. Scheidt, *Org. Lett.* **2003**, *5*, 3487–3490; b) Q. Yang, J. E. Ney, J. P. Wolfe, *Org. Lett.* **2005**, *7*, 2575–2578; c) C. Welter, A. Dahnz, B. Brunner, S. Streiff, P. Dübon, G. Helmchen, *Org. Lett.* **2005**, *7*, 1239–1242; d) F. A. Davis, H. Xu, Y. Wu, J. Zhang, *Org. Lett.* **2006**, *8*, 2273–2276.

[19] For examples of pyrrolidines in natural products, see: a) J. W. Daly, T. F. Spande, H. M. Garraffo, *J. Nat. Prod.* **2005**, *68*, 1556–1575; b) N. Asano, R. J. Nash, R. J. Molyneux, G. W. Fleet, *Tetrahedron: Asymmetry* **2000**, *11*, 1645–1680; J. D. Scott, R. M. Williams, *Chem. Rev.* **2002**, *102*, 1669–1730.

[20] Aminohydroxylation: a) D. W. Patrick, L. K. Truesdale, S. A. Biller, K. B. Sharpless, *J. Org. Chem.* **1978**, *43*, 2628–2638; diamination: b) A. O. Chong, K. Oshima, K. B. Sharpless, *J. Am. Chem. Soc.* **1977**, *99*, 3420–3426.

[21] T. J. Donohoe, K. M. P. Wheelhouse (née Gosby), P. J. Lindsay-Scott, P. A. Glossop, I. A. Nash, J. S. Parker, *Angew. Chem.* **2008**, *120*, 2914–2917; *Angew. Chem. Int. Ed.* **2008**, *47*, 2872–2875.

[22] For a related inverse electron-demand cycloaddition, see: L. R. Domingo, *Eur. J. Org. Chem.* **2000**, 2265–2272.

[23] M. Schröder, A. J. Neielson, W. P. Griffith, *J. Chem. Soc. Dalton Trans.* **1979**, 1607–1611.

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