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A Lewis Acid Promoted Oxidative Cyclization

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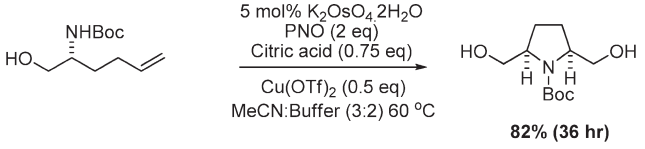
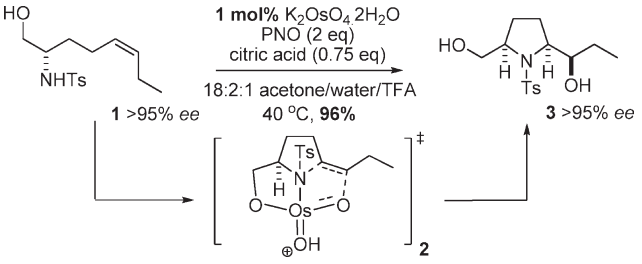


Replacing trifluoroacetic acid with a catalytic amount of Lewis acid in the osmium mediated oxidative cyclization results in higher yielding reactions that can proceed nearly an order of magnitude faster. The osmium loading can also be reduced to as little as 0.2 mol %. Furthermore, these mildly acidic conditions are capable of tolerating a wide range of acid sensitive protecting groups that are incompatible with previous cyclization conditions.

The oxidative cyclization of 1,5-dienes to the corresponding THFs has been known for almost 50 years. Previously, reports from our group showed that vicinal diols derived from 1,5-dienes will cyclize to form 2,5-*cis*-THFs in good yields under the action of osmium tetraoxide and an acid.[1] This system used trimethylamine *N*-oxide (TMO) as a reoxidant, and utilized an excess of a "sacrificial alkene", usually *trans*-cinnamic acid, in order to afford a source of Os(VI) in situ. This methodology has also been applied to unsaturated *N*-Ts amino-alcohols, which cyclize to give the corresponding 2,5-*cis*-pyrrolidines.[2]

Recently, it was also noted that pyridine *N*-oxide (PNO) could be used as a novel reoxidant for osmium in the oxidative cyclization of *N*-protected amino-alcohols.[3] It is speculated that PNO is capable of oxidizing Os(IV) to Os(VI) (this being the more active catalyst for the cyclization process) but not to unwanted Os(VIII)—which can result in the dihydroxylation

SCHEME 1. The Osmium-Mediated Oxidative Cyclization



of the starting material. As a consequence of this, PNO combined with citric acid (which stabilizes Os(VI) with respect to disproportion in acidic media)[4] has been incorporated as a replacement to the trimethylamine *N*-oxide/*trans*-cinnamic acid system in the amino-alcohol series to give higher yielding reactions (Scheme 1). As previously shown, the cyclization reactions are stereospecific (with *syn* addition of both heteroatoms across the tethered alkene) and stereoselective (forming *cis*-2,5-pyrrolidines exclusively).

Initial attempts to apply these improved conditions, using PNO/citric acid, to the more challenging diol cyclization to afford the corresponding tetrahydrofurans were unsuccessful, however, with more catalyst and TFA being required for the reaction to proceed cleanly. While still being a substantial improvement on the previous TMO/TFA conditions, the very acidic environment required for the cyclization to occur, both in the diol and the amino-alcohol series, leads to complications during workup, especially on a large scale. As a result, a wide range of functional groups were still not compatible with the reaction.

The exact role of acid in the cyclization step is unknown. However, it has been suggested that protonation of an oxo ligand on the osmium center results in the metal becoming electron deficient, which allows an inverse electron demand [4+2] cycloaddition to take place with an electron-rich alkene.[5] It was envisaged that in order to make the cyclization conditions less acidic, a catalytic amount of an oxophilic Lewis acid could be used in place of a Brønsted acid in the cyclization procedure. After screening a range of Lewis acids, we can now report that a range of metal triflates are capable of replacing the Brønsted acid, and cyclizing vicinal diols to THF rings.

Initial investigations concentrated on the cyclization of diol **4**. Under previous conditions the reaction proceeded to furnish **5** in 72% yield in 20 h (Table 1). Initial improvements to this were observed by changing the reoxidant to PNO, with the addition of citric acid. Furthermore, replacing TFA with an excess of Lewis acid in the form of $Sc(OTf)_3$ saw a further improvement in the yield; however, when used catalytically, $Sc(OTf)_3$ in acetone encouraged the formation of acetonide side products, and therefore, the

(1) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766–4768.

(2) Donohoe, T. J.; Churchill, G. H.; Wheelhouse, K. M. P.; Glossop, P. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 8025–8028.

(3) Donohoe, T. J.; Wheelhouse, K. M. P.; Lindsay-Scott, P. J.; Glossop, P. A.; Nash, I. A.; Parker, J. S. *Angew. Chem., Int. Ed.* **2008**, *47*, 2872–2875.

(4) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421–433.

(5) Previous attempts to heat the reactions in TFA saw an increase in the rate of reaction, but yields were generally lower: e.g., treating **6** under the PNO/TFA cyclization conditions with 1 mol % of $K_2OsO_2(OH)_4$ at rt furnished **7** in 74% after 24 h; however, at 60 °C the yield was only 51% after 14 h.

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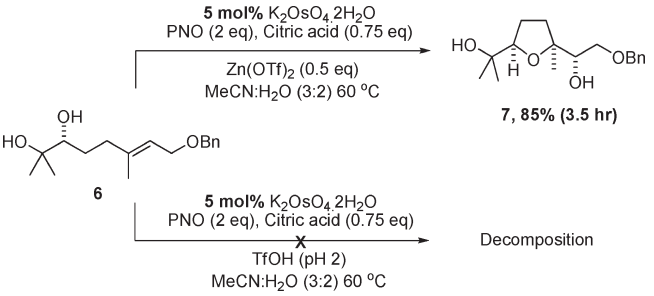
TABLE 1. Optimization of Conditions

entry	conditions	yield of **5**
1	5 mol % of $K_2OsO_4 \cdot 2H_2O$, TMO, *trans*-cinnamic acid, TFA, acetone:water (9:1)[a]	72% (20 h)
2	5 mol % of $K_2OsO_4 \cdot 2H_2O$, PNO, citric acid, TFA, acetone:water (9:1)[a]	78% (16 h)
3	5 mol % of $K_2OsO_4 \cdot 2H_2O$, PNO, citric acid, 6 equiv of $Sc(OTf)_3$, acetone:water (9:1)[a]	84% (16 h)
4	5 mol % of $K_2OsO_4 \cdot 2H_2O$, PNO, citric acid, 0.5 equiv of $Cu(OTf)_2$, MeCN:water (4:1), 60 °C	87% (8 h)
5	5 mol % of $K_2OsO_4 \cdot 2H_2O$, PNO, citric acid, 0.5 equiv of $Zn(OTf)_2$, MeCN:water (4:1), 60 °C	89% (8 h)
6	1 mol % of $K_2OsO_4 \cdot 2H_2O$, PNO, citric acid, 0.5 equiv of $Zn(OTf)_2$, MeCN:water (3:2), 60 °C	92% (6 h)
7	0.2 mol % of $K_2OsO_4 \cdot 2H_2O$, PNO, citric acid, 0.5 equiv of $Zn(OTf)_2$, MeCN:water (3:2), 60 °C	90% (72 h)

[a]Reaction carried out at room temperature

SCHEME 2. Triflate Source

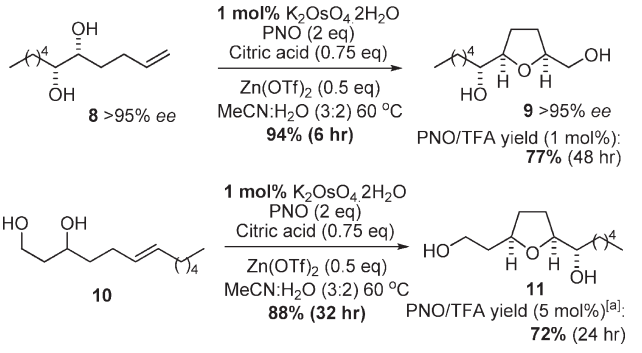


use of acetone as a solvent was abandoned. After screening various solvents and temperatures, an acetonitrile/water solvent system was found to be most effective. In addition to this, the reaction could be heated to 60 °C, resulting in an increase of the rate of reaction, with no loss in yield. This is completely unlike the previous TFA conditions, where heating led to deleterious side reactions.[5] Screening various metal triflates also revealed that $Cu(OTf)_2$ and $Zn(OTf)_2$ were cheaper, milder, and equally reliable alternatives to $Sc(OTf)_3$. Both $Cu(OTf)_2$ and $Zn(OTf)_2$ give similar yields (Table 1, entries 4 and 5), and are essentially interchangeable. Rates of reaction were also found to be much quicker when more water was added. Following the large increase in rate and comparatively mild nature of these new conditions, the loading of $K_2OsO_4 \cdot 2H_2O$ can now be reduced to as low as 0.2 mol % (Table 1, entry 7).

To establish the role of the $M(OTf)_x$ species, a series of trial reactions were conducted. Initially, it was unclear as to whether the Lewis acid acted by interacting with the intermediate osmate ester, or simply as a mild in situ source of TfOH. The pH of the Lewis acid-promoted cyclization was measured to be pH 2. Therefore, in an analogous reaction, the Lewis acid was omitted, and the reaction adjusted to pH 2 by addition of TfOH. After several hours, however, significant amounts of decomposition were seen, with only a trace of desired THF recovered (Scheme 2).

Investigations into the exact role of citric acid were conducted, as it was unclear whether the cyclization was facilitated due to a pH effect of the added acid, or due to the ligating α-hydroxy carboxylic acid moiety of the citrate species, which stabilizes the metal and encourages the cyclization by assisting product release.[4] To determine the importance of the two processes, two acids with similar pK_a values to citric acid were

SCHEME 3. Unhindered Substrates[a]



[a]When attempted with 1 mol % $K^2OsO_4 \cdot 2H_2O$ less than 50% conversion was observed after 96 h

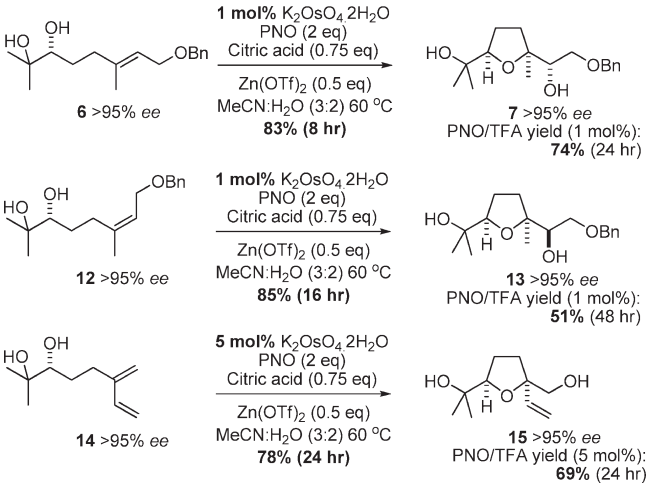
used in a standard cyclization reaction on geraniol benzyl ether **6**, glycolic acid (with an α-hydroxy carboxylic acid group) and acetic acid. The standard reaction with citric acid proceeded to completion in just 3.5 h. It was found that when replacing citric acid with glycolic acid (0.75 equiv) and adjusting the reaction to pH 2 with acetic acid, the reaction proceeded to completion in 9 h. Furthermore, when citric acid was replaced with just acetic acid at pH 2, the reaction took 96 h, thus allowing us to conclude that the most important role of the citric acid is the ligating effect of the α-hydroxy carboxylic acid, as originally suggested by Sharpless.[4]

When applying these new Lewis acid/citric acid conditions to relatively unsubstituted diol substrates, the cyclization proceeds with excellent yields to produce the corresponding THF, even in the case of 1,3 diols, which have previously been more reluctant to cyclize due to the slow formation of the intermediate osmate ester (Scheme 3).

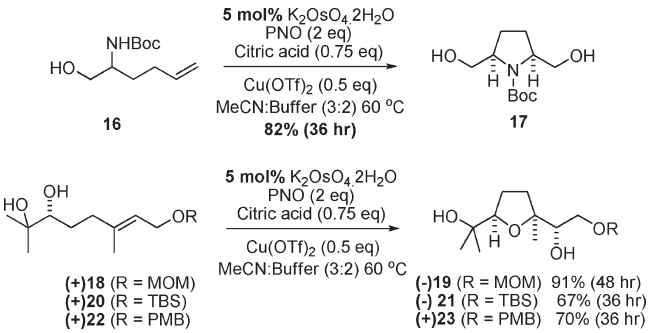
With these new conditions available, a range of challenging substrates that had previously cyclized in relatively low yields or did not cyclize at all were examined (Scheme 4).

Despite the PNO/TFA conditions proving a substantial improvement from the previous TMO/TFA system, cyclizing the same substrates by using the new Lewis acid conditions saw another increase in yield and in most cases the rate of reaction was also accelerated. However, a loading of 5 mol % was required to cyclize **14**, as polymerization of the diene occurs slowly on a time scale comparable to the cyclization reaction.

SCHEME 4. Substrates That Were Difficult To Cyclize



SCHEME 5. Acid-Sensitive Substrates



The main benefit, however, of removing TFA from the osmium-mediated oxidative cyclization procedure was to make the reaction compatible with a wide range of functional groups that would otherwise react under the harshly acidic conditions. It was found that the use of a phosphate buffer at pH 6.5 instead of water[6] was sufficient to tolerate a range of acid-sensitive *N*- and *O*-protecting groups (Scheme 5). Despite longer reaction times, the reactions proceeded cleanly in good to excellent yields. In each case, attempting to cyclize the same substrates under PNO/TFA conditions led to complete deprotection within 1 h, with no oxidative cyclization products being observed.

To conclude, replacing trifluoroacetic acid with a catalytic amount of a Lewis acid has afforded a mild procedure capable of forming both tetrahydrofurans and pyrrolidines in high yields. Furthermore, due to the mildly acidic conditions, the osmium loading can be reduced as low as 0.2 mol %. These conditions are now compatible with a wide range of acid-sensitive protecting groups.

Experimental Section

Representative Procedure 1. To a solution of diol (1 mmol) in acetonitrile (12 mL) and water (8 mL) was added pyridine *N*-oxide (2 mmol), citric acid (0.75 mmol), potassium osmate dihydrate (0.01 mmol) and the metal trifluoromethansulfonate (0.5 mmol). The resulting solution was warmed to 60 °C and the mixture was left to stir until all starting material had reacted. Sodium sulfite (5 mg) and water (10 mL) were added and the reaction was cooled to room temperature. The mixture was extracted with ethyl acetate (3 × 50 mL) and the combined organic layers were washed with 2 M HCl (20 mL), 3 M NaOH (20 mL), and brine (20 mL), dried over sodium sulfate, and filtered, then the solvent was removed in vacuo. The crude product was purified as specified.

(1*R*,1′*S*)-1,1′-((2*R*,5*S*)-Tetrahydrofuran-2,5-diyl)dipentan-1-ol, 5. Diol **4** (50 mg, 0.18 mmol) was subjected to procedure 1 (8 h). The crude product was purified by flash column chromatography [SiO_2, acetone−petrol, 20:80] to give THF **5** (various yields) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.86−3.79 (2H, m), 3.43−3.39 (2H, m), 3.00 (2H, br s), 1.97−1.88 (2H, m), 1.77−1.69 (2H, m), 1.48−1.28 (12H, m), 0.90 (6H, t, J = 10.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 82.9, 74.3, 33.7, 28.1, 27.8, 22.7, 14.1.

(*R*)-1-((2*R*,5*S*)-5-(Hydroxymethyl)tetrahydrofuran-2-yl)hexan-1-ol, 9. Diol **8** (50 mg, 0.27 mmol) was subjected to procedure 1 (6 h). The crude product was purified by flash column chromatography [SiO_2, acetone−petrol, 20:80] to give THF **9** (51 mg, 94%) as a colorless oil. IR (thin film, cm^{-1}) 3385, 1651, 1463, 1054; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.14−4.06 (1H, m), 3.83 (1H, dd, J = 6.6, 12.6 Hz), 3.75 (1H, dd, J = 11.6, 2.8 Hz), 3.51 (1H, dd, J = 11.6, 5.2 Hz), 3.46−3.40 (1H, m), 3.07 (2H, br. s), 1.99−1.88 (2H, m), 1.84−1.67 (2H, m), 1.57−1.17 (8H, m), 0.89 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 83.1, 80.0, 74.4, 65.1, 34.0, 31.9, 28.2, 27.2, 25.4, 22.6, 14.1; HRMS (ES$^+$, *m*/*z*) calcd 225.1461 ($C_{11}H_{22}NaO_3$), found 225.1462; $[\alpha]^{22}_D$ +9.5 (*c* 0.5, CH_2Cl_2).

(*R*)-1-((2*R*,5*S*)-5-(2-Hydroxyethyl)tetrahydrofuran-2-yl)hexan-1-ol, 11. Diol **10** (50 mg, 0.18 mmol) was subjected to procedure 1 (30 h). The crude product was purified by flash column chromatography [SiO_2, acetone−petrol, 15:85] to give THF **11** (49 mg, 88%) as a colorless oil. IR (thin film, cm^{-1}) 3386, 1464, 1067; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 4.07 (1H, dtd, J = 7.6, 7.2, 4.8 Hz), 3.81−3.76 (3H, m), 3.39 (1H, q, J = 5.6 Hz), 2.89 (1H, br s), 2.67 (1H, br s), 2.06−1.22 (14H, m), 0.87 (3H, t, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 82.9, 79.1, 74.1, 61.1, 37.7, 34.1, 31.9, 31.6, 27.5, 25.4, 22.6, 14.1; HRMS:(ES$^+$, *m*/*z*) calcd 239.1618 ($C_{12}H_{24}NaO_3$), found 239.1617.

2-((2*R*,5*S*)-5-((*S*)-Benzyloxy(hydroxy)methyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 7. Diol **6**[1] (50 mg, 0.18 mmol) was subjected to procedure 1 (8 h). The crude product was purified by flash column chromatography [SiO_2, acetone−petrol, 20:80] to give THF **7** (44 mg, 83%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39−7.26 (5H, m), 4.62−4.53 (2H, m), 3.85 (1H, t, J = 7.1 Hz), 3.74 (1H, dd, J = 8.5, 3.3 Hz), 3.69−3.63 (1H, m), 3.61−3.54 (1H, m), 3.20 (2H, br s), 2.28−2.17 (1H, m), 2.06−1.85 (2H, m), 1.65−1.58 (1H, m), 1.23 (3H, s), 1.15 (3H, s), 1.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 137.8, 128.5, 127.8, 85.8, 83.9, 75.4, 73.5, 71.7, 71.1, 35.1, 27.8, 26.3, 25.0, 23.3; $[\alpha]^{22}_D$ −15.0 (*c* 1.0, CH_2Cl_2).

2-((2*R*,5*S*)-5-((*R*)-Benzyloxy(hydroxy)methyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 13. Diol **12** (50 mg, 0.18 mmol) was subjected to procedure 1 (16 h). The crude product was purified by flash column chromatography [SiO_2, acetone−petrol, 20:80] to give THF **13** (45 mg, 85%) as a colorless oil. IR (thin film, cm^{-1}) 3398, 1071; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.39−7.26 (5H, m), 4.56 (2H, s), 3.88−3.80 (2H, m), 3.62 (1H, dd, J = 9.7, 3.2 Hz), 3.41 (1H, dd, J = 9.7, 7.8 Hz), 2.98 (2H, br s), 2.23−2.15 (1H, m), 2.05−1.85 (2H, m), 1.53 (1H, ddd, J = 12.4, 8.3, 6.8 Hz), 1.24 (3H, s), 1.16 (3H, s), 1.10 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 138.8, 128.5, 127.8, 84.9, 84.4, 75.5, 73.4, 71.8, 71.2, 32.7, 27.7, 26.6, 25.1, 23.6; HRMS (ES$^+$, *m*/*z*) calcd 317.1729 ($C_{17}H_{26}NaO_4$), found 317.1733; $[\alpha]^{22}_D$ +3.1 (*c* 1.0, CH_2Cl_2).

(6) The sodium phosphate buffer consisted of a 1:1 mixture of 0.67 M NaH_2PO_4 and 0.67 M Na_2HPO_4 (pH 6.5 at 22 °C): Zhao, M. M.; Li, J.; Mano, E.; Song, Z. J.; Tschaen, D. M. *Org. Synth.* **2005**, *81*, 195–203.

2-((2*R*,5*R*)-5-(Hydroxymethyl)-5-vinyltetrahydrofuran-2-yl)-propan-2-ol, 15. Diol **14**[7] (50 mg, 0.29 mmol) was subjected to procedure 1 (5 mol % Os, 16 h). The crude was purified by flash column chromatography [SiO_2, acetone−petrol, 20:80] to give **15** (39 mg, 78%) as a colorless oil. IR (thin film, cm^{-1}) 3375, 2967, 1056; ^1H NMR (400 MHz, $CDCl_3$) δ_H 5.80 (1H, dd, J = 17.2, 10.8 Hz), 5.31 (1H, dd, J = 17.2, 1.6 Hz), 5.13 (1H, dd, J = 10.8, 1.6 Hz), 3.84 (1H, t, J = 11.2 Hz), 3.59 (1H, d, J = 11.2 Hz), 3.49 (1H, d, J = 11.2 Hz), 3.10 (1H, br s), 2.94 (1H, br s), 2.11 (1H, ddd, J = 12.0, 8.8, 6.0 Hz), 1.97−1.82 (2H, m), 1.81−1.72 (1H, m), 1.29 (3H, s), 1.14 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 140.3, 114.0, 86.2, 85.7, 71.9, 67.5, 32.2, 27.6, 26.3, 25.1; HRMS (ES^+, m/z) calcd 209.1151 ($C_{10}H_{18}NaO_3$), found 209.1154; $[\alpha]_D^{22}$ +1.3 (*c* 1.0, CH_2Cl_2).

Representative Procedure 2. To a stirred solution of diol (1.0 mmol) in acetonitrile/pH 6.5 phosphate buffer (20 mL, 3:2 mixture) was added pyridine *N*-oxide (2.0 mmol), citric acid (0.75 mmol), and metal trifluoromethanesulfonate (0.5 mmol) before potassium osmate dihydrate (as specified) was added. The mixture was heated to 60 °C and left to stir until all starting material had reacted. The resulting mixture was then quenched with sodium sulfite (50 mg) and stirred for 0.5 h before ethyl acetate (50 mL) and water (20 mL) were added. The two layers were separated and the aqueous layer was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, and filtered, then the solvent was removed in vacuo. The crude product was purified as specified.

(2*R*,5*S*)-*tert*-Butyl 2,5-Bis(hydroxymethyl)pyrrolidine-1-carboxylate, 17. Amino-alcohol **16**[8] (50 mg, 0.23 mmol) was subjected to procedure 2. The crude product was purified by flash column chromatography [SiO_2, acetone−petrol,20:80] to give pyrrolidine **17**[9] (44 mg, 82%) as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ_H 4.54 (1H, br s), 4.04−3.72 (4H, m), 3.51 (2H, dd, J = 11.2, 4.8 Hz), 3.23 (1H, br s), 2.24−1.72 (4H, m), 1.47 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 155.4, 80.7, 64.4, 60.5, 28.5, 26.9.

2-((2*R*,5*S*)-5-((*S*)-1-Hydroxy-2-(methoxymethoxy)ethyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 19. Diol **18** (50 mg, 0.22 mmol) was subjected to procedure 2. The crude product was purified by flash column chromatography [SiO_2, acetone−petrol, 35:65] to give THF **19** (48 mg, 91%) as a colorless oil. IR (thin film, cm^{-1}) 3418 (br), 2972, 1464, 1378, 1151, 1035; ^1H NMR (400 MHz, $CDCl_3$) δ_H 4.66 (2H, s), 3.84 (1H, t, J = 7.2 Hz), 3.77 (1H, dd, J = 10.2, 2.8 Hz), 3.70−3.66 (1H, m), 3.55 (1H, dd, J = 10.2, 8.6 Hz), 3.38 (3H, s), 3.29 (1H, s), 3.22 (1H, s), 2.20 (1H, ddd, J = 12.4, 9.2, 6.0 Hz), 2.04−1.85 (2H, m), 1.62 (1H, ddd, J = 12.4, 8.6, 7.2 Hz), 1.23 (3H, s), 1.17 (3H, s), 1.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 96.9, 85.7, 83.9, 75.7, 71.7, 69.5, 55.4, 35.2, 27.7, 26.3, 25.0, 23.2; HRMS (ES^+, m/z) calcd 271.1516 ($C_{12}H_{24}NaO_5$), found 271.1514; $[\alpha]_D^{22}$ −5.2 (*c* 1.0, CH_2Cl_2).

2-((2*R*,5*S*)-5-((*S*)-2-(*tert*-Butyldimethylsilyloxy)-1-hydroxyethyl)-5-methyltetrahydrofuran-2-yl)propan-2-ol, 21. Diol **20** (50 mg, 0.17 mmol) was subjected to procedure 2. The crude product was purified by flash column chromatography [SiO_2, acetone−petrol, 20:80] to give THF **21** (35 mg, 67%) as a colorless oil. IR (thin film, cm^{-1}) 3396, 2958, 1471, 1257, 1115, 1069; ^1H NMR (400 MHz, $CDCl_3$) δ_H 3.87 (1H, dd, J = 7.2, 6.2 Hz), 3.79 (1H, dd, J = 9.2, 3.8 Hz), 3.69 (1H, ∼t, J = 9.2 Hz), 3.60 (1H, dd, J = 9.2, 3.8 Hz), 3.45 (1H, br s), 3.02 (1H, br s), 2.31 (1H, ddd, J = 12.4, 9.0, 7.2 Hz), 2.09−2.00 (1H, m), 1.97−1.87 (1H, m), 2.31 (1H, ddd, J = 12.0, 8.4, 6.2 Hz), 1.25 (3H, s), 1.16 (3H, s), 1.10 (3H, s), 0.92−0.90 (9H, m), 0.10−0.08 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 85.9, 83.5, 76.4, 71.8, 63.6, 35.1, 27.9, 26.0, 25.9, 25.0, 23.4, 18.3, −5.4, −5.3; HRMS (ES^+, m/z) calcd 341.2119 ($C_{16}H_{34}NaO_4Si$), found 341.2118; $[\alpha]_D^{22}$ −7.4 (*c* 1.0, CH_2Cl_2).

2-((2*R*,5*S*)-5-((*S*)-1-Hydroxy-2-(4-methoxybenzyloxy)ethyl-5-methyltetrahydrofuran-2-yl)propan-2-ol, 23. Diol **22** (100 mg, 0.32 mmol) was subjected to procedure 2. The crude product was purified by flash column chromatography [SiO_2, acetone−petrol, 20:80] to give THF **23** (74 mg, 70%) as a colorless oil. IR (thin film, cm^{-1}) 2971, 2872, 1712, 1612, 1514, 1249; ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.29−7.24 (2H, m), 6.91−6.86 (2H, m), 4.50 (2H, m), 3.85 (1H, t, J = 7.2 Hz), 3.81 (3H, s), 3.72 (1H, dd, J = 8.4, 3.2 Hz), 3.64 (1H, dd, J = 9.6, 3.2 Hz), 3.55 (1H, dd, J = 9.6, 8.4 Hz), 3.20 (1H, br s), 3.03 (1H, br s), 2.24 (1H, ddd, J = 12.4, 9.0, 6.4 Hz), 2.06−1.96 (1H, m), 1.94−1.85 (1H, m), 1.60 (1H, ddd, J = 12.4, 8.4, 7.2 Hz), 1.23 (3H, s), 1.15 (3H, s), 1.09 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 159.3, 129.9, 129.5, 113.9, 85.8, 83.9, 75.4, 73.1, 71.7, 70.7, 55.3, 35.1, 27.8, 26.3, 25.0, 23.3; HRMS (ES^+, m/z) calcd 347.1829 ($C_{18}H_{28}O_5Na$), found 347.1819; $[\alpha]_D^{22}$ −9.8 (*c* 1.0, CH_2Cl_2).

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Supporting Information Available: Preparation of compounds **4**, **8**, **10**, **12**, **18**, **20**, **24**, and ^1H NMR of all oxidative cyclization products are available. This material is available free of charge via the Internet at http://pubs.acs.org.

(7) Hioki, H.; Ooi, H.; Hamano, M.; Mimura, Y.; Yoshio, S.; Kodama, M.; Ohta, S.; Yanai, M.; Ikegami, S. *Tetrahedron* **2001**, *57*, 1235–1246.

(8) Anada, M.; Sugimoto, T.; Watanabe, N.; Nakajima, M.; Hashimoto, S. *Heterocycles* **1999**, *50*, 969–980.

(9) Chênevert, R.; Jacques, F.; Giguére, P.; Dassar, M. *Tetrahedron: Asymmetry* **2008**, *19*, 1333–1338.