Copper and silicon mediated, HMPA-free, n+3 ring expansions for the construction of medium sized lactones and lactams: short synthesis of (+)-*cis*-Lauthisan

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ARTICLE INFO

Article history:

Received

Received in revised form

Accepted

Available online

Keywords:

Medium Sized Lactones

Ketone Enolates

Epoxide Ring Opening

Ring Expansion

Total Synthesis

In this report, several new epoxide examples were united with β -silyl ketone enolates for the construction, after oxidative fragmentation, of ring expanded lactones, n+3 atoms in size. Importantly, azido lactones were found to be valuable in an extension of this protocol involving the n+3+p expansion into a series of hydroxy olefinic lactams. We also document a short, stereoselective total synthesis of (+)-*cis*-lauthisan and a new, cuprate-mediated and HMPA-free procedure for the generation of β -silyl silylenol ethers, useful in the environmentally-friendly construction of medium sized lactones.

1. Introduction

Pursuing our interest in epoxide ring opening reactions for the construction of medium sized lactones¹ and lactams,² we initiated a detailed investigation into our three-step, silicon-mediated n+3 ring expansion process with respect to substrate scope and overall efficiency. For example, the major advantage of this method over our previously reported two-step procedure³ was the replacement of toxic tin and lead reagents [LiSnBu₃ and Pb(OAc)₄, respectively] with environmentally-friendly sources of silicon (Me₃SiLi) and hypervalent iodine [PhI(OAc)₂, I₂]. Unfortunately, however, in order to generate the requisite β -silyl enolate, it was necessary to employ hexamethylphosphoramide (HMPA); a polar aprotic solvent which is known to be highly toxic. Also of note, a comprehensive substrate scope, in terms of reactive functionality on the epoxide sidechain, was not undertaken in either of our initial reports. Herein, we address both of these deficiencies and also provide a showcase for this method with the synthesis of ring expanded lactams and the stereoselective construction of (+)-*cis*-lauthisan.

2. Mechanistic Investigations

As mentioned above, the success of our n+3 ring expansion method relies upon the use of hypervalent iodine to fragment β -silyl hemiketal intermediates (cf. **1**, Scheme 1), formed *via* the union of β -silyl ketone enolates with epoxides, into lactones (cf.

2) with exclusively C(5)-C(6) *cis*-alkene geometry (n = 5 and 6). Said differently, when utilizing either cyclopent- or cyclohexenone as starting material, despite the *trans*-orientation between the hydrogens of their corresponding β -silyl hemiketals, we have not observed any *trans*-alkene containing lactone products.

Scheme 1. Hemiketal Oxidative Fragmentation and Lactone ORTEP

The observed stereochemical preference for this reaction was initially somewhat of a mystery, especially when one considers the anionic fragmentation mechanism that was operative in our earlier work³ and led to *trans*-alkenes as major products. Importantly, the *cis*-geometry was unambiguously confirmed in two ways: (1) *via* calculation of the alkene proton coupling

constant ($J = \sim 10$ Hz) of the resultant acyclic diols obtained after DIBAL-H reduction, and (2) the X-ray crystal structure of lactone **2a** which is representative of the 9-membered ring series (Scheme 1). On a related note, to the best of our knowledge, there have been no other literature reports that exploit the Suárez reaction conditions [$\text{PhI}(\text{OAc})_2$, I_2]⁴ for the oxidative fragmentation of a β -silyl hemiketal such as **1**.

After considering these data, as well as several literature reports concerning similar fragmentation reactions,⁵ we now propose the following, nonconcerted, fragmentation mechanism to account for *cis*-alkene formation (Scheme 2). In the absence of photochemical irradiation, hypoiodite **3**, formed upon the sequential addition of $\text{PhI}(\text{OAc})_2$ and I_2 to a solution of **1** in CH_2Cl_2 at 0°C , homolytically cleaves to form oxygen-centered radical **4** which subsequently undergoes bond scission to generate a lactone carbonyl and β -silyl carbon centered radical **5**. Previously, Kochi and coworkers observed that β -silyl radicals of this nature can be stabilized through hyperconjugation between the half filled radical *p*-orbital and the filled carbon–silicon σ -orbital.⁶ For this to occur in our system, carbon–carbon bond rotation must occur, resulting in an eclipsed conformation (**6**) before final fragmentation and olefin formation, orienting the C(5)-C(6) hydrogens *cis* to one another in the product (Scheme 2).

Scheme 2. Proposed Hemiketal Oxidative Fragmentation Mechanism

3. Construction of Novel 8-Membered Lactones

In addition to cyclohexenone, we have also reported that the β -silyl silylenol ether of cyclopentenone (**7**) can be exploited for the synthesis of 8-membered (5+3) lactones (cf. **9**, Scheme 3).¹ However, while reexamining our initial work, the substrate scope seemed somewhat limited, with silyl and benzyl protected alcohols the only reported functional groups tolerant of the two-step procedure. We now wish to report several additional reactive moieties that can survive both the epoxide opening step and subsequent oxidative fragmentation conditions (Scheme 3).

Several epoxide examples⁷ in Scheme 3 are noteworthy. In addition to chiral, non racemic epoxides (cf. **9a**),⁸ masked amine functionality, notably terminal nitriles (**9b**), aromatic nitro groups (**9c**), and azides (**9d-e**) are exceedingly competent. Two step yields for these lactones are generally good with the notable exception being allyl cyanide oxide, where the poor yield may be attributed to epoxide volatility and / or α -proton acidity.

Related to this study, we also united two new epoxide examples with the enolate corresponding to 6-membered enol ether **10** (Scheme 4).¹ Not surprisingly, 4-azidobutene oxide produced the desired lactone in comparable yield to **7** (cf. **2b** vs. **9d**),

Scheme 3. 5+3 Ring Expansion for the Construction of 8-Membered Rings

while a terminal aliphatic nitro group with acidic α -protons was also surprisingly able to withstand the reaction conditions.

Scheme 4. 6+3 Ring Expansion for the Construction of 9-Membered Rings

4. Lactone to Lactam Ring Expansions

In 2005, we published a short report regarding the sequential ring expansions of *n*-sized cycloalkenones into hydroxyolefinic *n*+3+*p* sized lactones,^{1b} where translactonization was efficiently triggered by fluoride mediated silyl ether cleavage. After the success of this work, we sought to develop an analogous protocol for the conversion of lactones into ring expanded lactams, especially in light of our related studies on the synthesis of δ -lactams *via* lactone ring contraction.² In a similar way, we had hoped that azido lactones **9d-e** and **2b** would serve as suitable substrates for this purpose.⁹

Initially, relying on the Corey method for azide reduction,¹⁰ lactone **2b** was treated with hydrogen over the Lindlar catalyst (Scheme 5). While the desired chemoselective reduction did occur, concomitant intramolecular reorganization was not observed; primary amine **11** was isolated as the major organic product (80%). This result is surprising, especially when one considers the transition state required for lactam formation is six atoms in size. A variety of subsequent reaction conditions were screened, for example: heat, microwave irradiation, base treatment (Et_3N and K_2CO_3), and the addition of Lewis acids (e.g., TiCl_4 , CeCl_3 , Me_3Al , and Al_2O_3), but unfortunately, this intermediate could not be driven to the desired 11-membered lactam product.

Undeterred by these results, we next sought to exploit 8-membered azido lactones **9d** and **9e** in a similar process. Pleasingly, by switching to the Staudinger conditions (PPh_3 and H_2O), azide reduction was directly followed by lactone to lactam ring expansion (cf. **9d** to **12** and **9e** to **13**) in good overall yield (Scheme 5). Unfortunately, when **2b** was treated with these same conditions,

lactone **11** was again isolated as the major organic product. While it is still unclear why amine **11** does not undergo ring expansion, one may argue that it could be due to the thermodynamic stability of a 9-membered lactone compared to the 11-membered lactam.¹¹ Further investigations into the scope and limitations of this new, four-step, synthesis of medium-sized lactams is ongoing, and will be reported in due course.

Scheme 5. n+3+p Lactone to Lactam Ring Expansions

5. Stereoselective Synthesis of (+)-*cis*-Lauthisan

Previously, we have exploited our ring expansion protocol for the short and efficient syntheses of medium sized lactones and piperidines.¹⁻² As an extension of these studies, we now wish to report the use of a 5+3 expansion as the key step in the total synthesis of (+)-*cis*-lauthisan [(+)-**16**], an easier to access saturated derivative of the marine derived cyclic ether (+)-laurencin.¹² Previous syntheses have suffered from long synthetic sequences (up to 18 steps), have been racemic, or proceeded with poor stereoselection.¹³ A notable exception is a recent study by Urbano and Carreño which produced the optical enantiomer, (–)-*cis*-lauthisan, in only four steps with high enantioselectivity *via* a reductive cyclization cascade.^{13j}

By uniting our ring expansion method with the elegant study by Nicolaou regarding carbanion addition to thionolactones,¹⁴ we have effected a stereoselective total synthesis of (+)-*cis*-lauthisan [(+)-**16**] in only six linear operations (Scheme 6). (+)-Hexenyl lactone (+)-**9a**, made in two steps (59%) from enol ether **7**, was first saturated and then converted, using the Lawesson reagent, to thionolactone (+)-**14**. In only two additional steps involving: (1) treatment with ethyl lithium, followed by iodomethane, and (2) reductive removal of sulfur, (+)-*cis*-lauthisan could be accessed in good overall yield (21% from **7**) and high enantioselectivity. Importantly, as determined by ¹H NMR, no trace of the undesired *trans*-oxocane was observed, with all data in good agreement with previous literature reports for this compound.

6. Copper-Mediated Conjugate Addition Studies

According to the original report by Still, the addition of Me₃SiLi-generated *via* the addition of MeLi to Me₃SiSiMe₃ in HMPA to cyclohexenone occurs smoothly (Scheme 7), with HMPA acting to stabilize the silyl anion and facilitate the 1,4-addition process.¹⁵ Wanting to find a more environmentally-friendly alternative, the use of comparable additives was explored. For example, tetramethylethylenediamine (TMEDA) and dimethyltetrahydropyrimidinone (DMPU) were separately substituted into the reaction, however, neither gave any evidence of the desired conjugate addition. In support of these findings, Fleming has reported that, trimethylsilyl lithium is difficult to generate in the absence of HMPA.¹⁶

Scheme 6. Stereoselective Total Synthesis of (+)-*cis*-Lauthisan

Since the trimethylsilyl anion proved troublesome to generate differently, it became necessary to explore complementary conditions that would allow for the necessary 1,4-addition of a silyl anion. Pleasingly, a search of the literature would prove useful in finding the appropriate anion and a method to perform the necessary conjugate addition.¹⁶ Of note, this method was also independently utilized by Hwu during a recent report regarding the conversion of enolates to β-silyl enones.¹⁷ Utilizing this procedure, we found that chlorodimethylphenylsilane could be treated with excess lithium metal, leading to a dark red solution of PhMe₂SiLi. After stirring ca. 18 h, the anion could be transferred, *via* canula, to a flame dried flask containing copper (I) iodide suspended in THF at –25 °C. After stirring for an additional 4 h, cyclohexenone could be added dropwise to the solution of silyl cuprate followed by Me₃SiCl and triethylamine after 30 min, forming the desired β-silyl silylenol ether (**17**, Scheme 7). Importantly, this compound was stable to routine aqueous work-up and flash column chromatography using florisil as stationary phase.

Scheme 7. Copper-Mediated, HMPA-free n+3 Ring Expansions

*Yields using **10** as starting material

Several aspects of this new protocol are noteworthy. In order to achieve reproducibly high yields, it was necessary to wash the CuI every two weeks using a soxhlet extractor (THF as solvent). As an alternative, CuI·SMe₂ could be substituted in place of CuI, however, the product enol ether retained an unpleasant odor, even after vacuum distillation. Comparable yields could also be achieved using diethylzinc (Et₂Zn) either in place of CuI, or with a catalytic amount of CuI added. Yields for this process were typically high (75–80%) and proceeded with the main advantage being a shorter reaction time overall, compared to the cuprate method. Also of note, β-silyl silylenol ether **17** is stable at –20 °C under nitrogen for at least several months and large quantities can

be generated and stored allowing one to consider it a stock reagent, utilized in small quantities, as needed.

When compared to the previously studied β -silyl silylenol ether **10**,^{1,2} the steric and electronic environment surrounding the β -silicon group of **17** is markedly different (Scheme 7). At the onset of this work, we were not sure that a lithium enolate derived from **17** could productively interact with a mono substituted epoxide. Pleasingly, when **17** was treated with MeLi at 0 °C, followed by cooling to -78 °C and the addition of 4-phenylbutene oxide and $\text{BF}_3 \cdot \text{Et}_2\text{O}$, a hemiketal was produced in high yield (77%). Importantly, when this intermediate was subsequently treated with $\text{PhI}(\text{OAc})_2$ and I_2 at 0 °C in CH_2Cl_2 , *cis*-alkene-containing lactone **2e** was isolated as the sole reaction product, in good overall yield (51% from **17**, Scheme 7). Encouraged by this result, two additional epoxides were screened in this new HMPA-free n+3 reaction sequence (Scheme 7, **2a** and **2d**), with yields being comparable, if not better than those observed using β -silyl silylenol ether **10** (yields in parentheses).

7. Conclusion

In this study, several new epoxide examples were united with β -silyl ketone enolates for the construction, after oxidative fragmentation, of ring expanded n+3 lactones. As an extension of this work, lactone to lactam ring expansion was investigated, as was the stereoselective total synthesis of (+)-*cis*-lauthisan. In a final note, a new, cuprate-mediated and HMPA-free protocol for the generation of a β -silyl silylenol ether is described, advancing this process even more towards a robust and environmentally-friendly procedure for the construction of medium sized lactones. Additional investigations by the Maio Laboratory are currently ongoing and will be reported in due course.

8. Acknowledgement

The authors would like to thank the NSF for seed support for this project, as well as Drs. Amy Sarjeant (JHU), Susan Hatcher (OSU), and Phil Mortimer (JHU) for providing analytical data services (X-ray and mass analysis). We would also like to thank Drs. Maxime Siegler (JHU) for data handling, Ryan Conyers (JHU) for coordinating data retrieval, and Alvin Kalinda (JHU) for his efforts regarding the reproducibility of our copper-mediated conditions. WAM dedicates this manuscript to his colleague and friend, Dr. James P. Bacci (1979–2015), with deep admiration and great respect.

9. Experimental Section

Unless otherwise noted, reactions were performed in flame or oven dried glassware under an atmosphere of dry argon. Reaction solvents (CH_2Cl_2 , THF, and Et_2O) were purified before use *via* distillation. All other solvents and reagents were purchased from Sigma-Aldrich and used as received, unless otherwise specified. Thin-layer chromatography (TLC) was performed using plates precoated with silica gel 60 Å F-254 (250 μm) and visualized by UV light, KMnO_4 , or anisaldehyde stains, followed by heating. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 (operating at 400 MHz and 100 MHz, respectively) or Varian XL-400 operating at the same frequencies, and are reported relative to residual solvent peak (δ 7.26 and δ 77.0 for ^1H and ^{13}C in CDCl_3). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Spectra obtained are described using the following abbreviations: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

General Procedure. An oven dried 25 mL roundbottomed flask was charged with β -silyl silylenol ether (1.0 mmol), dissolved in THF (1.5 mL) and cooled to 0 °C. To this was added MeLi (0.63 mL, 1.0 mmol, 1.6 M in Et_2O) dropwise, turning the solution a bright yellow color. After 5 min, the flask was then cooled to -78 °C before a solution of epoxide (0.5 mmol) in THF (1.5 mL) was added *via* cannula. The mixture was allowed to stir for 5 min before $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (60 μL , 0.5 mmol, neat) was added (1 drop every 4 sec) while cooling the needle with a piece of dry ice. After 30 min, the reaction was quenched with the addition of phosphate buffer (3.0 mL, pH 7.0) and allowed to warm to rt. The crude reaction mixture was then extracted with Et_2O (3 x 25 mL) and the combined organic layers dried over MgSO_4 and concentrated in vacuo. The crude product was purified by silica gel chromatography (90% hexanes, 10% ethyl acetate, ~1% Et_3N) to yield the desired hemiketal as a colorless oil which was taken directly on to the next step without further purification.

In a second step, an oven dried 25 mL roundbottomed flask was charged with hemiketal (0.1 mmol), dissolved in CH_2Cl_2 (8 mL) and cooled to 0 °C. To this solution was added, sequentially, $\text{PhI}(\text{OAc})_2$ (0.048 g, 0.15 mmol) and then I_2 (0.033 g, 0.13 mmol), turning the solution a dark purple color. The reaction was stirred for 5 hr at 0 °C before being quenched with a saturated aqueous solution of sodium thiosulfate, turning the solution a light pink color. The crude mixture was then extracted with CH_2Cl_2 (3 x 25 mL), and the combined organic layers were dried over MgSO_4 and concentrated in vacuo. The crude product was purified by silica gel chromatography (90% hexanes, 10% ethyl acetate) to afford the desired lactone as a colorless (often volatile) oil.

Lactone 2a. ^1H NMR (CDCl_3) δ 5.50-5.46 (m, 2H), 4.95-4.89 (m, 1H), 3.90-3.86 (m, 1H), 2.47-2.42 (m, 1H), 2.34-2.23 (m, 3H), 2.06-2.01 (m, 3H), 1.85-1.59 (m, 3H), 1.15 (d, J = 8.0 Hz, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (CDCl_3) δ 174.2, 134.4, 124.9, 70.9, 65.7, 45.0, 34.8, 33.6, 26.4, 25.9, 24.5, 18.0, -4.2, -4.8; IR (neat) 3011, 2953, 2930, 2857, 1743, 1448, 1359, 1257, 1139, 1107, 836 cm^{-1} ; HRMS (EI), m/z (M+Na) calcd. 335.2013 for $\text{C}_{17}\text{H}_{32}\text{O}_3\text{SiNa}^+$, found 335.2016. (note: unfortunately, the optical rotation for this compound was not obtained)

Lactone 2b. ^1H NMR (CDCl_3) δ 5.52-5.44 (m, 2H), 4.89-4.83 (m, 1H), 3.41-3.33 (m, 2H), 2.48-2.24 (m, 5H), 2.08-2.01 (m, 3H), 1.92-1.77 (m, 2H); ^{13}C NMR (CDCl_3) δ 174.2, 134.8, 124.3, 70.6, 40.0, 34.0, 33.7, 33.5, 26.4, 25.3; IR (neat) 2949, 2099, 1742, 1448, 1261, 1213, 1138, 727 cm^{-1} ; HRMS (FAB) m/z (M+H) calcd. 210.1243 for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_2^+$, found 210.1244.

Lactone 2c. ^1H NMR (CDCl_3) δ 5.50-5.46 (m, 2H), 4.78-4.72 (m, 1H), 4.38 (t, J = 6.8 Hz, 2H), 2.49-2.21 (m, 4H), 2.80-1.97 (m, 4H), 1.82-1.42 (m, 6H); ^{13}C NMR (CDCl_3) δ 174.5, 134.6, 124.5, 75.4, 72.6, 34.0, 33.6, 26.9, 26.5, 25.3, 22.5 (note: one carbon resonance is missing due to accidental overlap); IR (neat) 2951, 1737, 1552, 1448, 1356, 1215, 1139, 730 cm^{-1} ; HRMS (EI), m/z (M+Na) calcd. 264.1206 for $\text{C}_{12}\text{H}_{19}\text{NO}_4\text{Na}^+$, found 264.1200.

Lactone 2d. Has been reported previously by our laboratory. See reference 1b.

Lactone 2e. Has been reported previously by our laboratory. See reference 1a.

Lactone 9a. $[\alpha]_D^{23} +22.5^\circ$ ($c = 0.53$, CHCl_3); ^1H NMR (CDCl_3) δ 5.81-5.70 (m, 2H), 4.58-4.52 (m, 1H), 2.88-2.77 (m, 1H), 2.71 (ddd, $J = 13.2, 6.0, 2.8$ Hz, 1H), 2.46-2.38 (m, 1H), 2.29 (ddd, $J = 13.6, 11.6, 4.8$ Hz, 1H), 2.13-2.05 (m, 2H), 1.67-1.59 (m, 1H), 1.55-1.47 (m, 1H), 1.43-1.22 (m, 8H), 0.86 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 177.3, 132.5, 128.4, 78.4, 37.8, 34.7, 34.4, 31.7, 28.9, 25.7, 24.3, 22.5, 14.0; IR (neat) 3018, 2932, 2858, 1749, 1454, 1323, 1215, 1149, 1053 cm^{-1} ; HRMS (CI), m/z ($\text{M}+\text{Na}$) calcd. 233.1512 for $\text{C}_{13}\text{H}_{22}\text{O}_2\text{Na}^+$, found 233.1517.

Lactone 9b. ^1H NMR (CDCl_3) δ 5.90-5.72 (m, 2H), 4.83-4.77 (m, 1H), 2.87-2.62 (m, 6H), 2.38-2.31 (m, 1H), 2.25-2.14 (m, 1H); ^{13}C NMR (CDCl_3) δ 175.6, 134.0, 126.5, 116.1, 71.6, 37.6, 33.3, 24.3, 23.6; IR (neat) 2928, 2866, 2291, 1751, 1461 cm^{-1} ; HRMS (EI), m/z ($\text{M}+\text{Na}$) calcd. 188.0682 for $\text{C}_9\text{H}_{11}\text{NO}_2\text{Na}^+$, found 188.0691.

Lactone 9c. ^1H NMR (CDCl_3) δ 7.93-7.91 (m, 1H), 7.55-7.35 (m, 3H), 5.84-5.73 (m, 2H), 4.92-4.86 (m, 1H), 3.29-3.14 (m, 2H), 2.87-2.78 (m, 1H), 2.72-2.66 (m, 1H), 2.61-2.53 (m, 1H), 2.30-2.21 (m, 2H), 2.16-2.09 (m, 1H); ^{13}C NMR (CDCl_3) δ 176.6, 149.6, 133.0, 132.9, 132.6, 132.5, 127.8, 127.7, 124.7, 77.2, 37.6, 37.4, 34.4, 24.3; IR (neat) 2938, 1747, 1526, 1348, 1215, 1055 cm^{-1} ; HRMS (CI) m/z ($\text{M}+\text{Na}$) calcd. 284.0893 for $\text{C}_{14}\text{H}_{15}\text{NO}_4\text{SiNa}^+$, found 284.0890.

Lactone 9d. ^1H NMR (CDCl_3) δ 5.82-5.69 (m, 2H), 4.66-4.60 (m, 1H), 3.44-3.33 (m, 2H), 2.83-2.68 (m, 2H), 2.50-2.43 (m, 1H), 2.34-2.27 (m, 1H), 2.14-2.05 (m, 2H), 1.91-1.75 (m, 2H); ^{13}C NMR (CDCl_3) δ 176.7, 132.8, 127.7, 75.1, 47.9, 37.6, 34.2, 33.8, 24.2; IR (neat) 2939, 2100, 1748, 1215, 1057 cm^{-1} ; HRMS (EI), m/z ($\text{M}+\text{Na}$) calcd. 218.0899 for $\text{C}_9\text{H}_{13}\text{N}_3\text{O}_2\text{Na}^+$, found 218.0913.

Lactone 9e. ^1H NMR (CDCl_3) δ 5.82-5.69 (m, 2H), 4.57-4.52 (m, 1H), 3.35-3.30 (m, 2H), 2.87-2.68 (m, 2H), 2.50-2.42 (m, 1H), 2.33-2.26 (m, 1H), 2.13-2.02 (m, 2H), 1.80-1.59 (m, 4H); ^{13}C NMR (CDCl_3) δ 177.2, 132.8, 128.0, 77.5, 50.8, 37.7, 34.4, 31.5, 25.2, 24.3; IR (neat) 3030, 2946, 2872, 2097, 1743, 1454, 1314, 1211, 1146, 1053, 726 cm^{-1} ; HRMS (EI), m/z ($\text{M}+\text{Na}$) calcd. 232.1056 for $\text{C}_{10}\text{H}_{15}\text{N}_3\text{O}_2\text{Na}^+$, found 232.1048.

Lactone 11. A 10 mL roundbottomed flask was charged with lactone **2b** (0.006 g, 0.03 mmol) and the Lindlar catalyst (~0.002 g, 30% by weight) before being dissolved in ethanol (2 mL). The flask was then covered with a septa and evacuated using a vacuum pump, replacing the inner atmosphere with a blanket of hydrogen using a balloon. After 2 h the reaction mixture was diluted with CH_2Cl_2 (1 mL), passed over celite, and then concentrated in vacuo to afford the desired lactone as a colorless oil (0.004 g, 80%). ^1H NMR (CDCl_3) δ 5.49-5.47 (m, 2H), 4.89-4.84 (m, 1H), 2.49-2.22 (m, 5H), 2.08-1.88 (m, 3H), 1.83-1.73 (m, 2H), 1.43 (s, 2H). Because of the polar nature of this compound, it was protected as its BOC-derivative for further characterization.

A 15 mL roundbottomed flask was charged with **11** (0.029 g, 0.14 mmol) and dissolved in ethyl acetate (2 mL). To this was added the Lindlar catalyst (~0.005 g, 30% by weight) and BOC anhydride (0.036 g, 0.17 mmol). The flask was then covered with a septa and evacuated using a vacuum pump, replacing the inner atmosphere with a blanket of hydrogen using a balloon. After 5 h, the reaction mixture was diluted with CH_2Cl_2 (1 mL), passed over celite, and concentrated in vacuo. The crude product was purified by silica gel chromatography (70% hexanes, 30% ethyl acetate) to afford the desired BOC-protected lactone as a

colorless oil (0.036 g, 92%). ^1H NMR (CDCl_3) δ 5.49-5.46 (m, 2H), 4.82-4.76 (m, 1H), 3.38-3.32 (m, 1H), 3.08-3.03 (m, 1H), 2.48-2.21 (m, 4H), 2.07-1.97 (m, 3H), 1.82-1.73 (m, 3H), 1.42 (s, 9H) (note: the NH proton is likely overlapping with the chloroform peak at 7.26); ^{13}C NMR (CDCl_3) δ 174.6, 155.8, 134.6, 124.5, 79.2, 71.2, 37.1, 34.5, 33.9, 33.5, 28.3, 26.5, 25.3; IR (neat) 3413, 2981, 1811, 1742, 1716, 1512, 1371 cm^{-1} ; HRMS (EI), m/z ($\text{M}+\text{Na}$) calcd. 306.16757 for $\text{C}_{15}\text{H}_{25}\text{NO}_4\text{Na}^+$, found 306.16750.

Lactam 12. A 10 mL roundbottomed flask was charged with lactone **9d** (0.03 g, 0.2 mmol) and dissolved in THF (3 mL). To this was added PPh_3 (0.081 g, 0.23 mmol) and H_2O (0.1 mL) before the contents of the flask were heated to 50°C in an oil bath. After 18 hr, the reaction was concentrated in vacuo and columned directly without workup (92% CH_2Cl_2 , 7% MeOH, 1% NH_4OH) to afford the desired lactam as a colorless oil (0.018 g, 69%). ^1H NMR (CDCl_3) δ 5.60-5.53 (m, 3H), 4.13-4.04 (m, 1H), 3.49-3.40 (m, 1H), 3.19 (br s, 1H), 2.74 (br s, 1H), 2.38-1.99 (m, 5H), 1.85-1.61 (m, 2H), 1.26-1.07 (m, 1H); ^{13}C NMR (CDCl_3) δ 173.0, 129.7, 127.5, 69.4, 36.1, 34.2, 24.1 (note: two carbon resonances are missing due to accidental overlap.); IR (neat) 3300, 2927, 2853, 1640, 1547, 1444 cm^{-1} ; HRMS (EI), m/z ($\text{M}+\text{Na}$) calcd. 192.0995 for $\text{C}_9\text{H}_{15}\text{NO}_2\text{Na}^+$, found 192.0993.

Lactam 13. Was prepared in a similar manner to lactam **12**. ^1H NMR (CDCl_3) δ 5.77 (s, 1H), 5.63-5.53 (m, 2H), 3.88-3.87 (m, 1H), 3.23-3.14 (m, 2H), 2.38-2.04 (m, 6H), 1.66-1.24 (m, 4H); ^{13}C NMR (CDCl_3) δ 173.2, 129.6, 128.0, 77.2, 70.4, 39.8, 37.1, 31.5, 29.9, 25.2; IR (neat) 3300, 2927, 2862, 1640, 1556, 1454 cm^{-1} ; HRMS (FAB), m/z ($\text{M}+\text{H}$) calcd. 184.1338 for $\text{C}_{10}\text{H}_{18}\text{NO}_2^+$, found 184.1346.

Thionolactone 14. Lactone (+)-**9a** (0.128 g, 0.61 mmol) was placed in a 25 mL roundbottomed flask with THF (7 mL) along with palladium on carbon (~0.020 g, 20% by weight). The flask was then covered with a septa and evacuated using a vacuum pump, replacing the inner atmosphere with a blanket of hydrogen using a balloon. The reaction was monitored by GC and found to be complete after 15 h. The solution was then concentrated in vacuo to dryness and passed over a plug of silica using hexanes to afford the saturated lactone as a colorless oil (0.088 g, 70%). $[\alpha]_D^{25} +26.15^\circ$ ($c = 0.325$, CHCl_3); ^1H NMR (CDCl_3) δ 4.57-4.50 (m, 1H), 2.57-2.43 (m, 2H), 1.95-1.87 (m, 1H), 1.85-1.79 (m, 1H), 1.78-1.55 (m, 4H), 1.54-1.40 (m, 4H), 1.34-1.22 (m, 8H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 177.0, 78.7, 37.3, 35.6, 32.4, 31.7, 29.1, 28.9, 26.4, 25.7, 23.9, 22.5, 14.0; IR (neat) 2929, 2858, 1732, 1456, 1232, 1119, 1006 cm^{-1} ; HRMS (CI), m/z (M) calcd. 212.1770 for $\text{C}_{13}\text{H}_{24}\text{O}_2^+$, found 212.1785.

In a second setep, the saturated lactone (0.084 g, 0.40 mmol) was placed in a 25 mL roundbottom flask with toluene (2.5 mL, anhydrous) before the Lawesson reagent (0.160 g, 0.40 mmol) was added in one portion. The contents of the flask were then heated to reflux for 1 h and then allowed to slowly cool to rt. The cooled solution was then purified directly without workup (98% hexanes, 2% ethyl acetate) to afford the desired lactone as a colorless oil (0.064 g, 71%). $[\alpha]_D^{25} +17.22^\circ$ ($c = 1.15$, CHCl_3); ^1H NMR (CDCl_3) δ 4.80-4.84 (m, 1H), 3.18-3.12 (m, 1H), 3.00-2.93 (m, 1H), 2.02-1.67 (m, 6H), 1.66-1.55 (m, 2H), 1.54-1.40 (m, 2H), 1.38-1.22 (m, 8H), 0.87 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 229.1, 85.2, 44.1, 37.5, 35.6, 32.4, 31.6, 29.0, 26.2, 25.8, 24.0, 22.5, 14.0; IR (neat) 2926, 2360, 1458, 1302, 1232, 1081 cm^{-1} ; HRMS (CI), m/z (M) calcd. 228.1542 for $\text{C}_{13}\text{H}_{24}\text{OS}^+$, found 228.1554.

(+)-*cis*-Lauthisan (**16**). Thionolactone **14** (0.060 g, 0.26 mmol) was placed in a 25 mL roundbottomed flask with THF (3 mL) and then cooled to -78°C . To this solution was added ethyllithium (0.788 mL, 0.394 mmol, 0.5 M in cyclohexane/benzene) slowly *via* syringe. The reaction was allowed to stir for 10 min at -78°C before iodomethane (0.033 mL, 0.53 mmol) was added in one portion. After warming to rt, the reaction mixture was quenched with water and extracted with ether (3 x 25 mL). The combined organic layers were then dried over MgSO_4 and concentrated in vacuo. The crude material was purified by silica gel chromatography (95% hexanes, 5% ethyl acetate) to yield the desired cyclic ether as a colorless oil (0.055 g, 77%). This material was found to be unstable and taken directly on to the next step without characterization.

In a second step, this cyclic ether (0.045 g, 0.17 mmol) was placed in a 25 mL roundbottomed flask with toluene (5 mL, anhydrous) and treated with tributyltin hydride (0.111 mL, 0.41 mmol) and a catalytic amount of AIBN (0.005 g). The contents of the flask were then heated to reflux for 1.5 h after which the solution was cooled to rt, passed over a plug of silica gel using hexanes, and concentrated in vacuo. The crude reaction mixture was then purified by silica gel chromatography (95% hexanes, 5% ethyl acetate) to yield the desired compound as a colorless oil (0.035 g, 95%). $[\alpha]_{\text{D}}^{24} +14.6^{\circ}$ ($c = 0.15$, CHCl_3); ^1H NMR (CDCl_3) δ 3.44-3.38 (m, 1H), 3.36-3.30 (m, 1H), 1.82-1.56 (m, 5H), 1.55-1.33 (m, 9H), 1.32-1.20 (m, 8H), 0.93 (t, $J = 7.6$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (CDCl_3) δ 81.1, 79.6, 37.0, 33.6, 33.3, 31.9, 29.8, 29.5, 27.0, 26.3, 24.0, 22.6, 14.11, 10.9 (*note*: similar to known literature reports, two carbon resonances are missing due to accidental overlap. For example, see reference 13i); IR (neat) 2926, 2856, 1457, 1340, 1089 cm^{-1} ; HRMS (CI), m/z (M) calcd. 226.2291 for $\text{C}_{15}\text{H}_{30}\text{O}^+$, found 226.2284.

β -silyl silylenol ether 17. In an oxygen purged, nitrogen filled glove bag, lithium ribbon (0.51 g, 73.0 mmol) was carefully cut and added to a flame dried 100 mL flask. To this, was added chlorodimethylphenylsilane (1.78 g, 10.4 mmol) and THF (17 mL), which produced a dark red solution. After being allowed to stir at rt overnight (ca. 18 h), the silyl anion was transferred, *via* cannula, to a 50 mL roundbottom flask at -25°C containing freshly purified CuI (0.99 g, 5.2 mmol). After an additional 4 h of stirring, cyclohexenone (0.50 g, 5.2 mmol) in THF (3 mL) was added dropwise, followed by triethylamine (1.4 mL, 16.0 mmol) and trimethylsilyl chloride (2.0 mL, 16.0 mmol) after 30 min. Finally, after one additional hour of stirring, the reaction was warmed to 0°C and poured into a separatory funnel containing 100 mL of ice chilled hexanes. The organic layer was quickly washed, successively, with a saturated aqueous solution of NH_4Cl (2 x 40 mL), brine (30 mL) and deionized water (2 x 30 mL). The organic layer was then dried over MgSO_4 , filtered, and concentrated *in vacuo*. The crude product was purified by Florisil chromatography (70% hexanes, 30% ethyl acetate) to yield the desired β -silyl silylenol ether (**2**) as a slightly yellow oil (1.34 g, 85 %). ^1H NMR (CDCl_3) δ 7.59-7.54 (m, 2H), 7.44-7.37 (m, 3H), 4.89-4.88 (m, 1H), 2.02-1.98 (m, 2H), 1.81-1.71 (m, 3H), 1.59-1.55 (m, 1H), 1.39-1.34 (m, 1H), 0.35 (s, 3H), 0.34 (s, 3H), 0.23 (s, 9H); ^{13}C NMR (CDCl_3) δ 149.6, 138.2, 133.9, 128.9, 127.7, 104.7, 29.9, 23.7, 23.6, 23.5, 0.4, -4.8 , -4.9 . IR (neat) 3068, 2956, 2930, 2856, 1655, 1427, 1365, 1251, 1187, 1113, 1029, 987 cm^{-1} ; HRMS (EI) m/z (M) calcd. 304.1679 for $\text{C}_{17}\text{H}_{28}\text{OSi}_2^+$, found 304.1643.

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Copper and silicon mediated, HMPA-free, n+3 ring expansions for the construction of medium sized lactones and lactams: short synthesis of (+)-cis-Lauthisan

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