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Cyclopentanone Ring Expansion Leading to Functionalized δ-Lactams: Short Synthesis of Simple Sedum Alkaloids[†]

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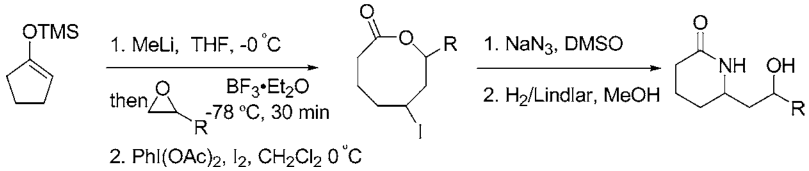
ABSTRACT



Monosubstituted epoxides react with (cyclopentenyloxy)trimethylsilane to afford, after subsequent oxidative fragmentation, a pair of diastereomeric 8-membered iodolactones. When these lactones are separately treated with sodium azide, followed by reduction over Lindlar's catalyst, lactone ring contraction yields 6-membered monosubstituted lactams. When (*R*)-1,2-epoxypentane is used in this 5 + 3 – 2 overall ring expansion sequence, one final step involving δ-lactam to piperidine reduction yields natural (–)-halosaline and (–)-epihalosaline in five steps and 12% and 23% overall yields, respectively.

For an organic chemist, the extent to which two molecules can be combined and manipulated seems almost limitless.[1] Small molecules are easily incorporated into larger ones in the construction of more and more complex synthetic targets. However, the development of new methodologies for combining easily obtainable starting materials remains an important goal.

Recently,[2] we reported a procedure in which *n*-sized 2-cycloakenones underwent $n + 3$ ring enlargement to produce medium-sized ring lactones. These homologous Baeyer−Villiger ring expansions resulted in the transformation of simple starting materials into more complex and valuable products. The key reaction of this four-step sequence involved an epoxide ring opening by a ketone enolate.[3] We now report a related $5 + 3 - 2$ overall ring expansion reaction sequence, with application to the construction of regiospecifically monosubstituted δ-lactams. Part of this multistep procedure is the synthetic equivalent of the Schmidt reaction,[4] a well-known organic transformation for the conversion of an *n*-sized cyclic ketone into an $n + 1$ ring enlarged lactam.

Epoxide ring opening by the lithium enolate of cyclopentanone, followed by oxidative fragmentation with hypervalent iodine[5] proceeded smoothly at 0 °C, in the absence of photochemical irradiation, with yields ranging from 37% to 62% (Scheme 1). Cyclopentanone enolate generated via

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[†] Dedicated to Professor Miguel Yus on the happy occasion of his 60th birthday.

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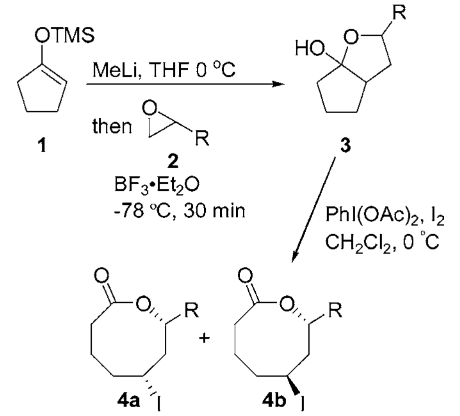
Scheme 1. 5 + 3 Cyclopentanone Ring Expansion Leading to Pairs of Diastereomeric Iodolactones



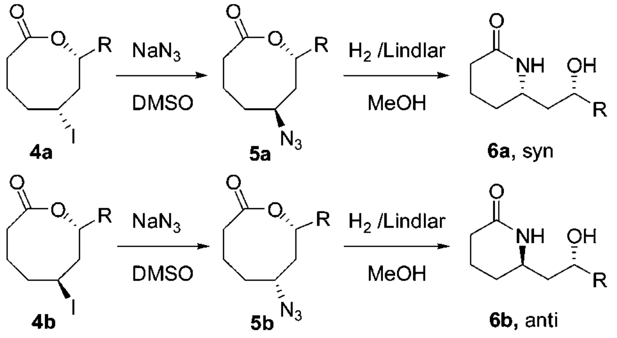
epoxide **2**, R	2 step yield	dr
2a, CH_2CH_2Ph	62%	2.0:1
2b, CH_2CH_2OTBS	39%	1.6:1
2c, $CH_2CH_2OCH_2Ph$	51%	2.0:1
2d, $CH_2CH_2C(CH_3)_2OTES$	37%	2.0:1
2e, $CH_2(CH_2)_4CH_3$	50%	2.0:1
2f, (*R*)-$CH_2CH_2CH_3$	61%	2.0:1

lithium diisopropylamide (LDA) deprotonation of freshly distilled cyclopentanone gave good but somewhat inferior results compared to those starting with (cyclopentenyloxy)-trimethylsilane (**1**). The product iodolactone pairs of diastereomers **4a** and **4b** are easily separable by column chromatography. When kept at 0 °C, these products have an indefinite lifetime. However, neat at room temperature, decomposition starts to occur within hours.

Nucleophilic displacement of iodides **4** with excess sodium azide in DMSO occurs with complete stereochemical inversion.[6] Yields for this step range from 60% to 85%, with the only byproduct being elimination of iodide to produce a mixture of allylic and homoallylic lactones. Hydrogenation of azides **5** over Lindlar's catalyst,[7] followed by the fast, in situ attack of the liberated primary amine on the lactone carbonyl, results in O-to-N ring contraction to form regiospecifically monosubstituted δ-lactams **6a** and **6b** in good overall yields (Scheme 2).[8]

The relative stereochemistry of the final products was determined by using X-ray crystallography. Lactams **6a** and **6b**, made with silyl ether epoxide **2b**, were desilylated and grown into needles by evaporation from ethanol.

Scheme 2. 8 − 2 Lactone-to-Lactam Ring Contraction



epoxide **2**, R	2 step yield	
	syn	*anti*
2a, CH_2CH_2Ph	74%	71%
2b, CH_2CH_2OTBS	59%	40%
2c, $CH_2CH_2OCH_2Ph$	46%	48%
2d, $CH_2CH_2C(CH_3)_2OTES$	64%	62%
2e, $CH_2(CH_2)_4CH_3$	71%	75%
2f, (*R*)-$CH_2CH_2CH_3$	76%	72%

From these results, we were able to conclude that the major product is *syn*, and the minor is *anti* (Figure 1). Formation of lactams **7a** and **7b** represents a novel access to dihydroxyalkyl δ-lactams.

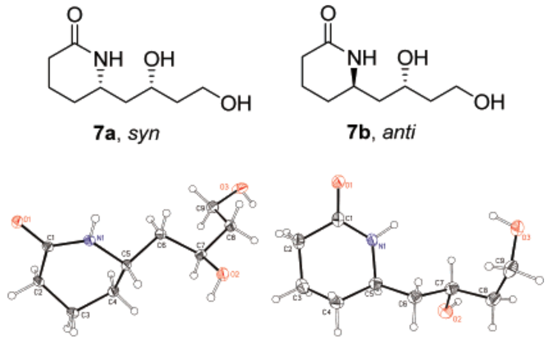


Figure 1. X-ray crystal structures showing syn and anti lactams.

These δ-lactams, which are easily accessible in four synthetic steps via this methodology, share a common core structure with the sedum alkaloid family,[9] which all contain a 2-(2′-hydroxyalkyl)piperidine unit. Twenty of these alkaloids have been isolated from the herb *Lobelia inflata*, commonly referred to as Indian tobacco; the American Indians smoked the plant's dried leaves because of the desirable effect some of these alkaloids had on their central nervous system.[10] Since their isolation, these alkaloids have shown a remarkable biological profile, being used in the treatment for nicotine drug abuse,[11] neurological disorders such as Alzheimer's[12] and Parkinson's,[12] learning dis-

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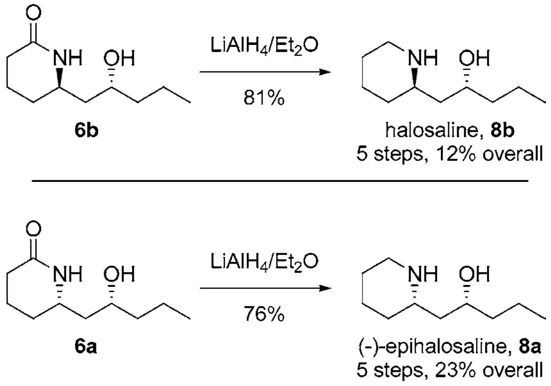
abilities,[10] asthma,[12] and anxiety.[11] Furthermore, the piperidine ring is found in many natural products,[12] and so the ability to produce these systems asymmetrically is of particular interest.

When (*R*)-1,2-epoxypentane[13] (**2f**) is used in our sequence, one additional step involving δ-lactam to piperidine reduction[14] yields natural (−)-halosaline (**8b**) and its isomer (−)-epihalosaline (**8a**) in five steps and 12% and 23% overall yields, respectively (Scheme 3).

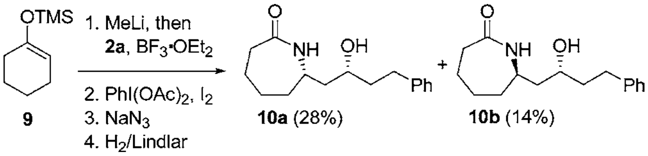
Scheme 3. Lactam Reduction



Previous syntheses of these two sedum alkaloids have involved many synthetic steps,[15] or two separations of diastereomeric intermediates,[16] or relatively complex and expensive starting material,[17] or 7−10 day reaction times.[18]

To increase the scope of this ring enlargement methodology, we have shown that the reaction is also adaptable to the construction of 7-membered ring lactams.[19] For example, commercially available (cyclohexenyloxy)trimethylsilane (**9**) was reacted with epoxide **2a** to produce 1-atom enlarged, regiospecifically monosubstituted ϵ-lactams **10a** and **10b**[20] (Scheme 4).

Scheme 4. 6 + 3 − 2 Cyclohexanone Ring Expansion Leading to a Pair of Diastereomeric Lactams



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[20] Compounds **10a** and **10b** exist as a nonseparable mixture of diastereomers. To separate them, it was necessary to functionalize the free alcohol in the lactam side chain as a *tert*-butyldimethylsilyl ether.

[21] **Typical procedure:** Formation of lactones **4a** and **4b** from epoxide **2f**: A 25 mL flask was charged with (cyclopentenyloxy)trimethylsilane (**1**) (0.300 g, 1.92 mmol) and dissolved in THF (1.5 mL). To this, at 0 °C, was added MeLi (1.26 mL, 2.02 mmol, 1.6 M in Et_2O) dropwise over the course of about 1 min. After 5 min, the reaction was cooled to −78 °C, and (*R*)-1,2-epoxypentane (**2f**) (0.083 g, 0.96 mmol) in THF (1.5 mL) was added via canula. The reaction was stirred for 5 min before $BF_3 \cdot Et_2O$ (0.122 mL,0.96 mmol, neat) was added very slowly (1drop/4 s), using a 100 μL syringe, while cooling the needle with a piece of dry ice. After 1 h, the reaction was quenched with phosphate buffer (3.0 mL, pH 7.0) and warmed to room temperature. The mixture was extracted with Et_2O (3 × 25 mL), and the combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (90% hexanes, 10% ethyl acetate, ~1% TEA) to give hemiketal **3** as a colorless oil. Hemiketal **3** (0.163 g, 0.96 mmol) was placed in a 50 mL flask with CH_2Cl_2 (16 mL) and the solution was cooled to 0 °C. To this was added $PhI(OAc)_2$ (0.339 g, 1.05 mmol) and then I_2 (0.243 g, 0.96 mmol, crystals). The reaction immediately turned dark purple. The reaction was stirred for 5 h at 0 °C before being quenched with a saturated solution of sodium thiosulfate. The mixture was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organics were dried over $MgSO_4$ and concentrated in vacuo. The crude product was purified by silica gel chromatography (90% hexanes, 10% ethyl acetate) to give lactones **4a** and **4b** (0.172 g, 2 steps—61%) as a 2:1 separable mixture of diastereomers. Major, 40%: ^{1}H NMR ($CDCl_3$) δ 4.67−4.61 (m, 1H), 4.21−4.15 (m, 1H), 2.72−2.66 (m, 1H), 2.54−2.26 (m, 5H), 1.96−1.86 (m, 2H), 1.67−1.58 (m, 1H), 1.50−1.29 (m, 3H), 0.09 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.9, 80.1, 65.8, 51.5, 41.6, 37.1, 31.8, 28.6, 26.0, 18.5, 13.6; IR (neat, cm^{-1}) 2960, 2870, 1711, 1357, 1252, 1056, 1008; HRMS (FAB) *m/z* (M + H$^+$) calcd for $C_{10}H_{18}O_2I^+$ 297.03516, found 297.03492; $[\alpha]^{25}_D$ 48.83 (*c* 0.056, $CHCl_3$). Minor, 20%: ^{1}H NMR ($CDCl_3$) δ 4.55−4.49 (m, 1H), 4.34−4.38 (m, 1H), 2.74−2.66 (m, 1H), 2.48−2.42 (m, 1H), 2.37−2.33 (m, 2H), 2.17−2.12 (m, 2H), 2.00−1.90 (m, 2H), 1.74−1.67 (m, 1H), 1.53−1.20 (m, 3H), 0.92 (t, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 175.1, 78.3, 48.9, 37.1, 36.9, 31.2, 28.2, 27.8, 18.6, 13.7; IR (neat, cm^{-1}) 2958, 2871, 1727, 1459, 1242, 1120, 1023; HRMS (FAB) *m/z* (M + H$^+$) calcd for $C_{10}H_{18}O_2I^+$ 297.03516, found 297.03480; $[\alpha]^{25}_D$ −6.95 (*c* 0.029, $CHCl_3$). Formation of azido lactone **5b** from iodolactones **4b**: A 15 mL flask was charged with lactone **4b** (0.030 g, 0.10 mmol), DMSO (1 mL), and 4Å mol sieves. The flask was warmed to 40 °C before sodium azide (0.066 g, 1.0 mmol) was added and the solution was allowed to stir at this temperature overnight. After 24 h, the reaction was quenched with water, extracted with dichloromethane (2 × 25 mL), dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by silica gel chromatography (90% hexanes, 10% ethyl acetate) to give lactone **5b** as a colorless oil (0.015 g, 71 %). ^{1}H NMR ($CDCl_3$) δ 4.81−4.75 (m, 1H), 3.50−3.43 (m, 1H), 2.49−2.38 (m, 2H), 2.16−2.11 (m, 1H), 1.99−1.87 (m, 5H), 1.71−1.67 (m, 1H), 1.56−1.37 (m, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 176.1, 76.9, 60.9, 43.1, 37.4, 33.8, 32.8, 26.4, 18.6, 15.3, 13.7; IR (neat, cm^{-1}) 2959, 2874, 2094, 1738, 1456, 1249, 1153; HRMS (FAB) *m/z* (M + H$^+$) calcd for $C_{10}H_{18}N_3O_2^+$ 212.13990, found 121.13905; $[\alpha]^{25}_D$ 29.49 (*c* 0.008, $CHCl_3$). Formation of lactam **6b**: A 10 mL flask was charged with azido lactone **5b** (0.022 g, 1.04 mmol), methanol (1 mL), and Lindlar's catalyst (0.19 g, 1.04 mmol). A rubber septum was then placed over the flask and the atmosphere inside was removed under vacuum before being placed under an atmosphere of hydrogen via a balloon. After 24 h the reaction mixture was diluted with ethyl acetate (5 mL) and passed over a short column of celite 545 with a thin layer of silica gel on top. The column was washed with EtOAc (100 mL) and concentrated in vacuo to give lactam **6b** as a colorless oil (0.017 g, 90 %). ^{1}H NMR ($CDCl_3$) δ 7.44 (s, 1H), 3.96 (s, 1H), 3.88−3.82 (s, 1H), 3.73−3.68 (m, 1H), 2.39−2.22 (m, 2H), 1.89−1.80 (m, 2H), 1.76−1.61 (m, 2H), 1.55−1.32 (m, 6H), 0.92 (t, J = 3.6, 3H); ^{13}C NMR ($CDCl_3$) δ 172.9, 67.8, 49.3, 42.6, 39.4, 31.0, 29.0, 19.4, 19.0, 14.0; IR (neat, cm^{-1}) 3302, 2953, 2871, 1655, 1467, 1411, 1351, 1308; HRMS (FAB) *m/z* (M + H$^+$) calcd for $C_{10}H_{20}NO_2^+$ 186.14940, found 186.14959.

In summary, this 4- or 5-step methodology[21] allows construction of valuable lactam products from simple starting materials. The transformations are straightforward and easily reproducible, which make this a viable method to prepare piperidine alkaloids in the sedum family, with control of absolute stereochemistry. Further investigation into the scope and limitations of this reaction sequence and application to novel alkaloid drug targets are currently in progress.

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Note Added after ASAP Publication. The stereochemical assignment of epoxide **2f** was incorrect in the version published ASAP June 12, 2007; the corrected version was published June 18, 2007.

Supporting Information Available: Experimental procedures and spectral data for all compounds, as well as CIF data for compounds **7a** and **7b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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