Asymmetric *Syn*-Selective Aldol Reactions of γ-Oxygenated Vinylogous Urethane with a Second Generation Chiral Auxiliary: Application in Construction of (+)-3-Deoxy-D-*manno*-2-octulosonic Acid

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Various examples of highly diastereoselective aldol reactions are presented where the nonracemic lithium enolate **6** derived from a C4-oxygenated vinylogous urethane reacts in *syn* fashion to provide upon intramolecular lactonization useful γ-alkoxy-δ-lactone synthons **12a**−**f**. In one particular example, the result of reaction with an acrolein surrogate, the lactone product **12e** is applied in an efficient asymmetric synthesis of (+)-KDO (10 steps, 34% overall yield). Notable transformations include (1) hydrolysis of the vinylogous urethane functionality, (2) stereoselective reduction of the resulting β-keto-lactone **2**, (3) stereoselective dihydroxylation of the vinyl side chain of δ-lactone **17**, and (4) addition of α-ethoxy-vinyllithium to the lactone carbonyl of **19** to procure the aldulosonic acid residue in **1** upon ozonolysis.

Introduction

The merit of four-carbon enolates has been demonstrated in many prior synthetic applications.[1] Enolates derived from acyclic vinylogous urethanes, in particular, offer malleable functionality upon aldol and acylation reactions.[2] In a previous communication,[3] we disclosed a highly *syn*-selective second generation vinylogous urethane (VU), **5**, carrying a C4 methyl substituent, which uses a simple and readily prepared nonracemic auxiliary. From X-ray work,[4] on a species closely related to **7**, we had speculated that the lithium enolate possessed the structure indicated in Figure 1. The unique structure of these enolate aggregates, in particular their very real lithium−nitrogen bond, suggested to us that changing the C4 methyl substituent to an oxygen residue would not perturb the overall structure of these systems. Thus, we anticipated that the vinylogous urethane **3** (R′ = $O(CH_2)_2TMS$) would form the enolate structure **6** and thereby provide *syn*-products as its alkyl analogue (R′ = CH_3) had in similar aldol reactions.

The contiguous array of hydroxyl residues in (+)-3-deoxy-D-*manno*-2-octulosonic acid, (+)-KDO (**1**), presented a challenging target to test our proposed modification.[5,6] Scheme 1 illustrates that the β-keto-lactone **2**, a potential precursor of **1**, might be derived from lactone

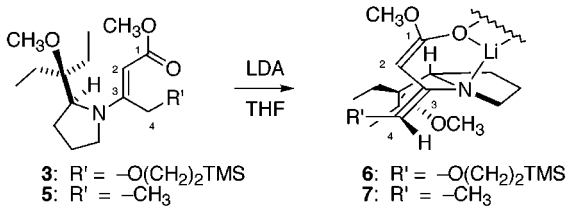
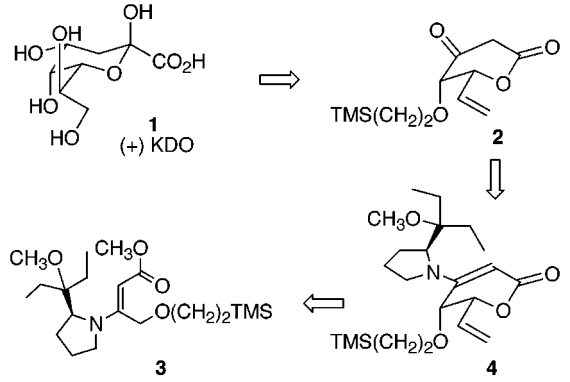


Figure 1.

Scheme 1



4 by hydrolytic removal of the amine residue, and **4** in turn would result from a *syn*-selective aldol reaction of **3** with acrolein. Herein, we describe the aldol reactions of

† Dedicated to the memory of Professor R. H. Schlessinger, deceased On December 11, 1997.

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(2) For selected examples, see: (a) Dankwardt, S. M.; Dankwardt, J. W.; Schlessinger, R. H. *Tetrahedron Lett.* **1998**, *98*, 4983−4986. (b) Schlessinger, R. H.; Li, Y.-J. *J. Am. Soc. Chem.* **1996**, *118*, 3301−3302. (c) Schlessinger, R. H.; Gillman, K. W. *Tetrahedron Lett.* **1996**, 37, 1331−1334. (d) Schlessinger, R. H.; Tata, J. R.; Springer, J. P. *Tetrahedron Lett.* **1987**, *28*, 5423−5426 and references therein.

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(5) (+)-KDO occurs in the lipopolysaccharide (LPS) region of the cell membrane of all Gram-negative bacteria. It provides a unique link between the hydrophobic lipid A and the hydrophilic polysaccharide subunits. Interruption of the biosynthesis of **1** leads to a buildup of LPS precursors and prevents the growth of these types of bacteria. Anderson, L.; Unger, F. M.; Eds. *Bacterial Lipopolysaccharides: Structure, Synthesis, and Biological Activities*; ACS Symposium Series 231; American Chemical Society: Washington, DC, 1983.

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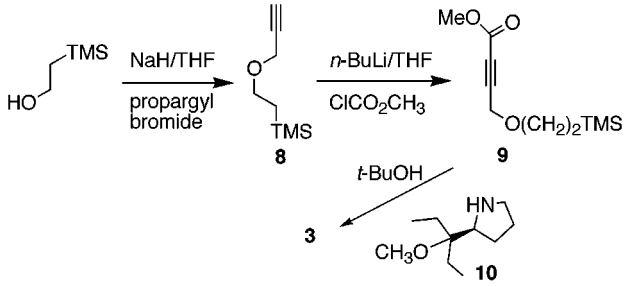
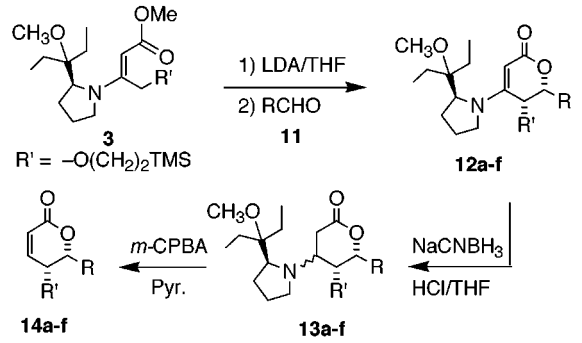
Scheme 2



Scheme 3



vinylogous urethane **3** with a variety of aldehydes and demonstrate potential applications of this methodology by an asymmetric synthesis of (+)-KDO (**1**).

Results and Discussion

Our synthesis of vinylogous urethane **3**, Scheme 2, started with 2-(trimethylsilyl)ethanol which was deprotonated with sodium hydride. The resulting sodium alkoxide coupled with propargyl bromide to afford the ether **8** (91%).[7] Deprotonation of alkyne **8** with *n*-BuLi and subsequent treatment with methyl chloroformate produced the acetylene ester **9** (85%). Last, **9** was reacted with the nonracemic amine, **10**, to afford vinylogous urethane **3** in 91% yield.[8]

The enolate **6**, obtained by deprotonation of **3** with LDA/THF (−78 → 0 → −78 °C), was condensed with aldehydes **11a**−**f** to afford the corresponding vinylogous urethane lactones **12a**−**f** (Scheme 3). These materials were then converted into their corresponding α,*β*-unsaturated lactone analogues **14a**−**f** in a two-step sequence for purposes of determining the overall stereoselection. Utilizing a Borch reduction, lactones **12a**−**f** were treated with $NaCNBH_3$ in acidic media to afford their corresponding *β*-amino lactone analogues **13a**−**f**.[9] These compounds were in turn converted into their unsaturated lactone counterparts **14a**−**f** by treatment with *m*-CPBA and then pyridine. HPLC analyses of **14a**−**f** using normal phase 3 *μ*m Spheriosorb silica gel and 5 *μ*m Chiralcel OD stationary phases provided both the diastereomeric and enantiomeric ratios for each lactone when compared to a racemic standard of *syn* and *anti* products.[10] The results are given in Table 1.

Table 1

entry no.	aldehyde RCHO no.	R	VU Lactone **12** no.	yield, %	α,*β*-unsaturated lactone **14** no.	de, %	ee, %
1	**11a**	*t*-Bu	**12a**	93	**14a**	97.2	96.5
2	**11b**	*i*-Pr	**12b**	73	**14b**	99.3	96.6
3	**11c**	Ph	**12c**	84	**14c**	97.9	98.4
4	**11d**	(*E*)-CH=CHCH$_2$CH$_3$	**12d**	78	**14d**	98.7	96.5
5	**11e**	(*E*)-CH=CHSnBu$_3$	**12e**	76	**14e**	98.5	96.8
6	**11f**	(*Z*)-CH=CHSnBu$_3$	**12f**	75	**14f**	98.9	97.7

Upon establishing that the C4-oxygenated vinylogous urethane **3** indeed afforded lactone products with excellent de values, we set out to demonstrate the absolute stereochemistry for these systems by the synthesis of (+)-KDO. Unfortunately, condensation of the lithium enolate **6** with acrolein resulted in the formation of intractable tars. Thus, we turned to the use of (*E*)-3-(tri-*n*-butylstannyl)-2-propenal, **11e**, as an acrolein equivalent.[11] Starting with the vinylogous urethane lactone **12e**, we converted this material into the *β*-keto lactone **2** (in 78% yield) by HCl hydrolysis of the vinylogous urethane functionality together with concomitant protodestannylation of the vinyl stannane residue (Scheme 4).

Hydride reduction under Luche's conditions gave the hydroxy lactol **15** as a single stereoisomer.[12] This compound in turn was treated with Ag_2CO_3 on Celite to obtain the hydroxy lactone **16** (80%, two steps).[13] Many other reduction conditions were attempted, but none were found to be both regio- and stereospecific; hence, the transformation was accomplished in the above two-step procedure.

We next chose to remove the *β*-trimethylsilyl ether protecting group of **16** using $BF_3{\cdot}Et_2O$ and to then protect the resulting diol product as its corresponding acetonide **17** for easier isolation (78%, two steps). The stage was now set to install the diol side chain required by **1**. Gratifyingly, catalytic osmylation of **17**, seemingly distributed between the two reactive conformers **17a** and **17b**, gave **18** as the sole product.[14] The diol portion of **18** was protected as its acetonide to afford **19** (90%, two steps).

Finally, the problem of adding a carboxylic acid to the lactone carbonyl group of **19** was addressed. After considerable difficulty with other nucleophilic surrogates, the α-ethoxy vinyllithium (EVL) was found to smoothly

(7) When either silicon (OTBS) or allyl (OCH$_2$CH=CH$_2$) or benzyl (OCH$_2$C$_5$H$_5$) were used as the C4-oxygen protecting group in vinylogous urethane **3**, these systems suffered either from oxygen−oxygen silyl migration or 2,3-Wittig rearrangements, respectively. Dankwardt, S. M. Ph.D. Thesis, University of Rochester, 1992.

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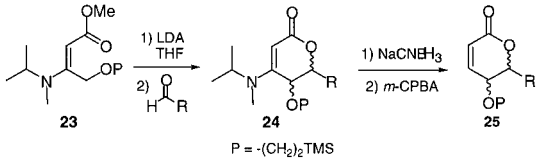
(10) The de and ee values of **14a**−**f** and hence of the VU lactones **12a**−**f** were determined by comparison with a racemic mixture of the *syn* and *anti* forms of the lactone **25**, which was prepared from vinylogous urethane **23** as shown below. Under typical conditions, lactone **24** was produced in 3: 1 *syn*:*anti* selectivity. It's interesting to note that while the vinylogous urethane derived from pyrrolidine or dimethylamine is *anti*-selective, vinylogous urethane derived from *tert*-butylamine or diisopropylamine is *syn*-selective.

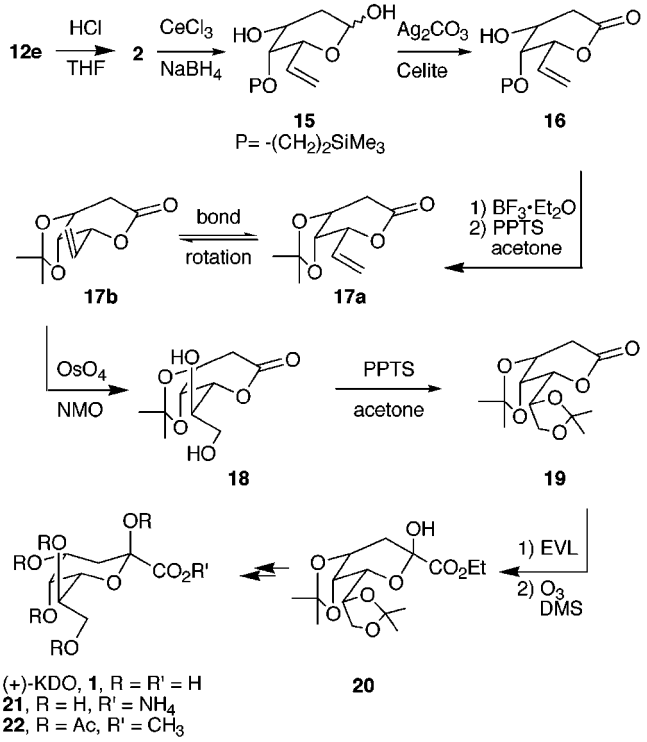


(11) (a) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851. (b) Evans, D. A.; Gage, J. R. *J. Org. Chem.* **1992**, *57*, 1957.

(12) (a) Felkin−Ahn reduction predicts hydride addition to occur opposite the α-axial C−O bond of **2**. (Macromodel 3.5a) minimization of the α-keto lactone **2** predicted the boat form of the lactone with the adjacent protected hydroxy group at C4 occupying an axial position on the ring. (b) Gamal, A. L.; Luche, J. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.

(13) Fetizon, M.; Golfier, M.; Mourgues, P. *Tetrahedron Lett.* **1972**, 4445−4448.

Scheme 4



add (1.1 equiv, 0.45 M in THF, −78 °C, 30 min) to lactone **19**.[15] Reductive ozonolysis provided the ethyl ester **20** (86% overall). Removal of the isopropylidene groups from **20** proceeded in a straightforward manner by treatment with 90% aqueous acetic acid at 90 °C for 45 min. Hydrolysis of the ethyl ester (0.1 N NaOH, 2 h), followed by adjustment of acidity to pH = 3 (Dowex-50W-X4), furnished (+)-KDO, **1**, isolated as the crystalline ammonium salt **21** (89% overall yield, mp 123−126 °C, $[\alpha]^{21}_D$ = +39.5° (*c* 1.2, H_2O)).[16] For the purpose of further characterization and comparison, the ammonium salt **21** was converted to its peracetylated methyl ester **22** ($[\alpha]^{21}_D$ = +99.7° (*c* 1.2, MeOH); lit.[17] $[\alpha]^{21}_D$ = +101° (*c* 1.0, MeOH)) according to literature procedure and again shown to be identical in every spectroscopic respect to that reported as derived from naturally occurring **1**.[17]

Conclusion

The pliant functionality of vinylogous urethane-derived enolates has been demonstrated by a concise synthesis of (+)-KDO. Noteworthy steps include (a) stereospecific reduction of *β*-keto-lactone, (b) stereospecific osmylation of an olefinic side chain, and (c) the use of ethoxyvinyllithium as a surrogate for a trialkyl orthoformate anion in the nucleophilic addition to lactone. The high *syn*-selectivity (97%−99% de) obtained from the reaction of lithium enolate derived from vinylogous urethane **3** with a wide range of aldehydes further substantiates the very real lithium−nitrogen bond in these types of enolate systems and suggests that the aggregate **6** is the reacting species that provides the good enantioselectivities (96%−98% ee) achieved from this second-generation chiral auxiliary. It is hoped that these easily accessible malleable systems will find applications in future asymmetric endeavors.

Experimental Data

General Information. The following solvents were distilled directly before use, under a slight positive pressure of nitrogen. Diethyl ether, tetrahydrofuran, and benzene were distilled from sodium benzophenone ketyl. *tert*-Butyl alcohol was distilled from calcium hydride. The chloroform, methylene chloride, isopropyl alcohol, and hexanes used for infrared spectra, HPLC analyses, and optical rotations were labeled spectroscopic grade by the manufacturer. Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR were recorded at 300 and 75.5 MHz, respectively, and chloroform was used as internal standard. Infrared spectra were recorded on a Perkin-Elmer 1600 series Fourier transform infrared spectrometer. Chiral stationary-phase HPLC analyses were performed with a Varian 3010 pump and LDC spectromonitor using Chiralcel OJ columns supplied by J. T. Baker. The spectra was recorded with a LDC Ultra-Violet/Visible recording spectrometer. Mass spectra were analyzed by the Midwest Center for Mass Spectrometry and UCS Mass Spectrometry Facility. Microanalyses were done by Microlytics, Dr. Greg Dabkowski, P.O. Box 199, South Deerfield, MA 01373.

***β*-(Trimethylsilyl)ethyl Propargyl Ether (8).** Sodium hydride (32.1 mmol, 0.81 g, dry, 95% weight) was suspended in THF (20 mL) and cooled to 0 °C. 2-(Trimethylsilyl)ethanol (20.1 mmol, 2.88 mL) was added to above solution dropwise. Deprotonation continued at 0 °C for 10 min and room temperature for 1 h. Then propargyl bromide (21.0 mmol, 1.87 mL) was added slowly followed by addition of catalytic amount of tetrabutylammonium iodide. The reaction was continued at room temperature for 1 h and then refluxed for 4 h. After this 5 h period, the reaction was quenched with sat. NH_4Cl and extracted with ether. The combined organic layers were dried with $MgSO_4$ and filtered, the solvent was removed, and the product **8** distilled (65 °C, 26 mmHg) to yield a colorless oil (2.85 g, 91% yield). IR ($CHCl_3$) 3306, 2955, 1352, 1250, 1181, 1079. ^{1}H NMR ($CDCl_3$) δ 4.14 (d, 2 H, J = 2.41 Hz), 3.61 (t, 2 H, J = 8.32 Hz), 2.42 (t, 1 H, J = 2.41 Hz), 0.97 (t, 2 H, J = 8.32 Hz), 0.04 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 73.8 C, 67.3 CH_2, 67.1 CH, 57.3 CH_2, 17.9 CH_2, −1.4 CH_3. R_f = 0.85 (hexane:EtOAc/2:1). HRMS calcd for $C_8H_{16}OSi$: 156.0970, molecular ion not observed, found: $(M - C_3H_9Si)^+$ 83.0496, $(M - C_5H_7O)^+$ 73.0471. Anal. Calcd for C 61.48, H 10.32. Found: C 61.51, H 10.34.

Methyl 4-[*β*-(Trimethylsilyl)ethoxy]-2-butynoate (9). Ether **8** (14.5 mmol, 2.27 g) was dissolved in 10 mL of THF and cooled to −78 °C. *n*-Butyllithium (15.9 mmol, 10.2 mL, 1.57 M solution in hexanes) was slowly added to the cold solution. The reaction mixture was warmed to 0 °C and stirred for 1 h. The mixture was chilled to −78 °C, and methyl chloroformate (17.4 mmol, 1.40 mL) was added dropwise. The reaction was stirred for 30 min at −78 °C, warmed to 0 °C,

(14) A Monte Carlo conformational search over a 50 kJ range with 50 steps produced the two minimum energy conformers of **17** to be that represented by the boat structures **17a** and **17b**, and predicted **17a** to be 2.5 kJ/mol more stable than **17b**. **17b** in turn was more stable than the next conformer, which if reactive, would have provided the unobserved osmylation product. It appeared that dihydroxylation of either **17a** from the convex face, or **17b** anti-periplanar to the allylic C−O bond, would result in the desired side chain alcohol stereochemistry represented by **18**. The stereoselectivity was assumed to be greater than 95% as ^{1}H NMR showed only one diastereomer. For explanation of stereoselectivity, see: (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Karabatsos, G. J.; Fenglio, D. J. *Topics in Stereochemistry*; Wiley-Interscience: New York, 1970; Vol. 5, p 167.

(15) The α-ethoxy vinyllithium species was prepared in a manner similar to that described for the α-methoxy vinyllithium species. See Baldwin, J. E.; Hofle, G. A.; Lever, O. W. *J. Am. Chem. Soc.* **1974**, *96*, 7125. For the addition of similar vinyllithium species to ketones, see Chavdarian, C. G.; Heathcock, C. H. *J. Am. Chem. Soc.* **1975**, *97*, 3822.

(16) Authentic Sample from Sigma Co. has mp 122−125 °C, $[\alpha]^{21}_D$ = +40.9° (*c* 0.9, H_2O); lit. (see reference 6c) mp 121.5−123 °C, $[\alpha]^{21}_D$ = +42.4° (*c* 1.7, H_2O).

(17) Charon, D.; Szabo, L. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2369−2374.

and stirred 45 min. After being warmed to room temperature and stirred 90 min longer, the reaction was quenched with excess sat. NH_4Cl. The mixture was extracted with ether, and the combined organic layers were dried over anhydrous $MgSO_4$. After removal of solvent, the residue was distilled under vacuum (115 °C, 1 mmHg) to yield compound **9** (2.64 g, 85% yield) as a colorless liquid. IR ($CHCl_3$) 2955, 1715, 1436, 1260. ^{1}H NMR ($CDCl_3$) δ 4.26 (s, 2 H), 3.80 (s, 3 H), 3.62 (t, 2 H, J = 8.31 Hz), 0.97 (t, 2 H, J = 8.31 Hz), 0.04 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 153.5 CO, 84.1 C, 68.0 CH_2, 57.2 CH_2, 54.5 C, 52.6 CH_3, 17.9 CH_2, −1.4 CH_3. R_f = 0.7 (hexane:EtOAc/2:1). HRMS calcd for $C_{10}H_{18}O_3Si$: 214.1025, molecular ion not observed. Found: 213.0947 for $(M - H)^+$, 19.0791 for $(M - CH_3)^+$.

Vinylogous Urethane 3. A solution of ester **9** (5.60 mmol, 1.20 g) in *tert*-butyl alcohol (5 mL) was heated to reflux, and amine **10** (6.44 mmol, 1.10 g) was added. After 2 h, the reaction was cooled to ambient temperature, and the volatiles were removed to yield a yellow oil. The oil was Kugelrohr distilled (3×10^{-6} Torr, 180 °C) to give compound **3** as a very viscous pale yellow oil (1.96 g, 91% yield). $[\alpha]^{21}_D$ = +222.4° (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3019, 2949, 2884, 1681, 1573. ^{1}H NMR ($CHCl_3$) δ 5.40 (d, 1 H, J = 11.87 Hz), 4.71 (br, 1 H), 4.50 (d, 1 H, J = 11.87 Hz), 4.30 (br, 1 H), 3.60 (s, 3 H), 3.55 (m, 2 H), 3.35 (br, 2 H), 3.14 (s, 3 H), 1.78−1.97 (m, 4 H), 1.60−1.43 (m, 4 H), 0.94−0.80 (m, 8 H), 0.05 (s, 9 H). ^{13}C ($CHCl_3$) δ 168.9 CO, 160.5 C, 88.4 CH, 81.6 C, 67.3 CH_2, 63.5 CH_2, 62.7 CH, 50.7 CH_2, 50.1 CH_3, 49.8 CH_3, 26.6 CH_2, 26.3 CH_2, 26.1 CH_2, 23.6 CH_2, 18.4 CH_2, 8.2 CH_3, 7.6 CH_3, −1.4 CH_3. Anal. Calcd for $C_{20}H_{39}NO_4Si$: C 62.30, H 10.19, N 3.63. Found: C 62.44, H 9.98, N 3.49.

General Procedure for Preparation of Vinylogous Urethane Lactone 12a−f. To a solution of vinylogous urethane **3** (1.00 mmol, 0.39 g) in anhydrous THF (1 mL) at −78 °C was added LDA (1.10 mmol, 1.1 mL of 1 M solution in THF). The mixture was stirred at −78 °C for 30 min and then warmed to 0 °C for 20 min and finally cooled to −78 °C for 20 min. After this period of 70 min, a solution of aldehyde (1.30 mmol) in anhydrous THF (0.5 mL) was added. Stirring was continued at −78 °C for 1 h followed by 0 °C for 30 min. The reaction was quenched with sat. NH_4Cl, extracted with EtOAc, dried over $MgSO_4$, and concentrated. The crude yellow oil was chromatographed (hexane:EtOAc/2:1 to 3:1) to yield VU lactone **12a−f** as pale yellow oils.

12a (93% yield): $[\alpha]^{21}_D$ = −73.41° (*c* 1.7, $CHCl_3$); IR ($CHCl_3$) 3020, 2961, 1660, 1584, 1467. ^{1}H NMR ($CDCl_3$) δ 5.21 (s, 1 H), 4.32 (d, 1 H, J = 1.65 Hz), 4.07 (m, 1 H), 3.89 (m, 1 H), 3.76 (d, 1 H, J = 1.95 Hz), 3.64 (m, 1 H), 3.30 (m, 2 H), 3.21 (s, 3 H), 2.1−1.5 (m, 8 H), 1.15 (s, 9 H), 0.90 (m, 8 H), −0.03 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 169.1 CO, 155.9 C, 88.4 CH, 86.2 CH, 82.1 C, 69.1 CH, 64.4 CH, 62.7 CH_2, 50.0 CH_3, 48.1 CH_2, 34.1 C, 26.9 CH_2, 26.4 CH_3, 26.1 CH_2, 23.7 CH_2, 18.9 CH_2, 8.5 CH_3, 7.7 CH_3, −1.5 CH_3. R_f = 0.55 (hexane:EtOAc/2:1). Anal. Calcd for $C_{24}H_{45}NO_4Si$: C 65.56, H 10.32, N 3.19. Found: C 65.76, H 10.48, N 3.22.

12b (73% yield): $[\alpha]^{21}_D$ = 119.9° (*c* 0.90, $CHCl_3$); IR ($CHCl_3$) 3030, 2968, 1661, 1585, 1415. ^{1}H NMR ($CDCl_3$) δ 5.24 (s, 1 H), 4.20 (d, 1 H, J = 2.40 Hz), 4.08 (m, 1 H), 3.91 (dd, 1 H, J = 2.42, 8.34 Hz), 3.65 (m, 1 H), 3.45 (m, 1 H), 3.30 (m, 1 H), 3.21 (s, 3 H), 2.2−1.5 (m, 9 H), 1.16 (d, 3 H, J = 6.57 Hz), 1.04 (d, 3 H, J = 6.66 Hz), 0.88 (m, 8 H), −0.01(s, 9 H). ^{13}C NMR ($CDCl_3$) δ 168.5 CO, 155.8 C, 88.7 CH, 85.0 CH, 82.1 C, 68.5 CH, 64.4 CH, 63.3 CH_2, 50.1 CH_3, 48.3 CH_2, 28.8 CH_2, 26.8 CH_2, 26.4 CH_2, 26.3 CH_2, 23.8 CH_2, 19.5 CH_3, 19.0 CH_2, 18.7 CH_3, 8.6 CH_3, 7.7 CH_3, −1.4 CH_3. R_f = 0.52 (hexane:EtOAc/2:1). HREI: calcd 425.2961 for $C_{23}H_{43}NO_4Si$, molecular ion not observed, found: 410.2744 for $(M - CH_3)^+$, 396.2571 for $(M - C_2H_5)^+$, 382.2423 for $(M-C_3H_7)^+$, 73.0473 for $(C_3H_9Si)^+$.

12c (84% yield): $[\alpha]^{21}_D$ = −132.4° (*c* 0.83, $CHCl_3$); IR ($CHCl_3$) 3027, 3017, 3005, 2973, 2884, 1669, 1586, 1454. ^{1}H NMR ($CDCl_3$) δ 7.56−7.28 (m, 5 H), 5.37 (s, 1 H), 5.37 (s, 1 H), 4.14 (m, 2 H), 3.94 (m, 1 H), 3.72 (m, 1 H), 3.44 (m, 1 H), 3.31 (m, 1 H), 3.25 (s, 3 H), 2.15−1.6 (m, 8 H), 0.92 (m, 6 H), 0.64 (t, 2 H, J = 8.30 Hz), −0.18 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 168.0 CO, 157.7 C, 136.4 C, 128.3 CH, 128.1 CH, 126.3 CH, 87.6 CH, 82.1 C, 80.1 CH, 74.1 CH, 67.8 CH_2, 64.3 CH, 50.2 CH_3, 48.7 CH_2, 26.9 CH_2, 26.4 CH_2, 23.7 CH_2, 18.8 CH_2, 8.6 CH_3, 7.8 CH_3, −1.6 CH_3. R_f = 0.44 (hexane:EtOAc/2:1). HRMS calcd 459.2805 for $C_{26}H_{41}NO_4Si$, found: 459.2808 for M^+, 430.2426 for $(M - C_2H_5)^+$, 73.0475 for $(C_3H_9Si)^+$.

12d (78% yield): $[\alpha]^{21}_D$ = −90.1° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3023, 2969, 2883, 1665. ^{1}H NMR ($CDCl_3$) δ 6.00 (m, 1 H), 5.7 (m, 1 H), 5.17 (s, 1 H), 4.70 (d, 1 H, J = 6.40 Hz), 4.03 (d, 1 H, J = 2.55 Hz), 3.90 (m, 2 H), 3.65 (m, 2 H), 3.36(m, 1 H), 3.21 (s, 3 H), 2.20−1.52 (m, 10 H), 1.05 (t, 3 H, J = 7.47 Hz), 0.90 (m, 8 H), −0.00 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 168.0 CO, 156.5 C, 136.9 CH, 124.2 CH, 123.3 CH, 88.1 CH, 82.1 C, 79.9 CH, 72.2 CH, 63.5 CH_2, 50.5 CH_3, 48.5 CH_2, 27.2 CH_2, 26.8 CH_2, 26.2 CH_2, 24.1 CH_2, 21.2 CH_2, 19.5 CH_2, 13.1 CH_3, 8.5 CH_3, 7.7 CH_3, −1.4 CH_3. R_f = 0.46 (hexane:EtOAc/2:1). Anal. Calcd for $C_{24}H_{43}NO_4Si$: C 65.86, H 9.90, N 3.20. Found: C 65.86, H 9.92, N 2.99.

12e (75% yield): $[\alpha]^{21}_D$ = −60.1° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3034, 2958, 1666, 1586, 1463. ^{1}H NMR ($CDCl_3$) δ 6.55 (dd, 1 H, J = 1.15, 19.16 Hz), 6.16 (dd, 1 H, J = 5.13, 19.16 Hz), 5.15 (s, 1 H), 4.72 (m, 1 H), 4.11 (d, 1H, J = 2.39 Hz), 3.87 (m, 2 H), 3.59 (t, 2 H, J = 8.02 Hz), 3.33 (m, 1 H), 3.19 (s, 3 H), 1.8−2.1 (br, 4 H), 1.75−1.2 (m, 17 H), 0.93−0.8 (m, 22 H), −0.03 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 167.9 CO, 156.5 C, 141.3 CH, 132.9 CH, 83.1 CH, 82.1 CH, 81.8 C, 71.9 CH, 65.3 CH_2, 64.2 CH, 50.0 CH_3, 48.5 CH_2, 29.0 CH_2, 27.3 CH_2, 26.8 CH_2, 26.4 CH_2, 26.3 CH_2, 23.7 CH_2, 19.0 CH_2, 13.6 CH_3, 9.4 CH_2, 8.5 CH_3, 7.7 CH_3, −1.4 CH_3. R_f = 0.72 (hexane:EtOAc/3:1). Anal. Calcd for $C_{34}H_{65}NO_4SiSn$: C 58.45, H 9.37, N 2.01. Found: C 58.50, H 9.35, N 1.96.

12f (76% yield): $[\alpha]^{21}_D$ = −88.4° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3020, 2956, 2928, 1669, 1585, 1463. ^{1}H NMR ($CDCl_3$) d 6.75 (dd, 1 H, J = 7.25, 13.20 Hz), 6.30 (d, 1 H, J = 13.18 Hz), 5.14 (m, 1 H), 4.52 (m, 1 H), 3.98 (d, 1 H, J = 2.19 Hz), 3.91−3.81 (m, 2 H), 3.73−3.62 (m, 2 H), 3.33 (m, 1 H), 3.19 (s, 3 H), 2.13−1.80 (br, 4 H), 1.75−1.20 (m, 17 H), 0.93−0.8 (m, 22 H), −0.01 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 166.8 CO, 156.4 C, 142.3 CH, 134.9 CH, 88.4 CH, 82.2 CH, 82.0 C, 72.9 CH, 65.8 CH_2, 64.3 CH, 49.6 CH_3, 48.4 CH_2, 27.0 CH_2, 26.8 CH_2, 26.7 CH_2, 26.6 CH_2, 26.3 CH_2, 23.6 CH_2, 19.0 CH_2, 13.3 CH_3, 10.8 CH_2, 8.3 CH_3, 7.6 CH_3, −1.5 CH_3. R_f = 0.75 (hexane:EtOAc/3:1). Anal. Calcd for $C_{34}H_{65}NO_4SiSn$: C 58.45, H 9.37, N 2.01; found: C 58.79, H 9.51, N 2.07.

General Procedure for Preparation of α,β-Unsaturated Lactone 14a−f. At room temperature, sodium cyanoborohydride (2.80 mmol, 0.19 g) was added to a solution of vinylogous urethane lactone **12a−f** (0.40 mmol) with a trace amount of bromocresol in THF (1.0 mL). HCl (0.5 mL of 2 M solution in THF) was added dropwise, and the deep blue solution turned yellow. The reaction was continued for 3 h, and the HCl/THF solution was added periodically to maintain the yellow color through out this period. Aqueous NaOH (2 M) was added until the solution turned deep blue. The mixture was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under vaccum to afford crude **13** as a yellow oil which was used in next step without further purification.

To a solution of crude **13** in THF (1 mL) at −78 °C was added *m*-CPBA (1.2 equiv, 98 mg, 85 wt %). After the reaction was stirred at −78 °C for 10 min and then 0 °C for 10 min, pyridine (0.60 mmol, 0.05 mL) was added. The stirring was continued at 0 °C for 10 min and room temperature for 30 min. The reaction was quenched with sat. aqueous $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Chromatography of the residue afforded the α,β-unsaturated lactone **14** as either colorless or pale yellow oil.

The diastereomeric ratio and enantiomeric ratio of the α,β-unsaturated lactone **14a−f** were analyzed with a Chiralcel OD and a Sherisorb column 38575 (3 μm), respectively. Since the α,β-unsaturated lactone was a degradation product of the vinylogous urethane lactone, the de% and ee% of compounds

14a−**f** represented the diastereoselectivity and enantioselectivity of the aldol reactions of the VU lithium enolate and the aldehydes.

The retention times of the diastereomers (*anti* and *syn*) and enantiomers (minor and major) were assigned by comparing the HPLC behaviors of the α,β-unsaturated lactones **14a**−**f** with racemic compound **25** (a degradation product of the racemic vinylogous urethane lactone **24**). Four peaks were seen when compound **14** was analyzed with the chiral column due to two anti- and two syn-compounds, while only two peaks were seen when analyzed with the Sherisorb column due to anti- and syn-diastereomers.

14a (76% yield): $[\alpha]^{21}_D = -278.5°$ (*c* 1.5, $CHCl_3$). IR ($CHCl_3$) 3021, 2960, 1719, 1261. ^{1}H NMR ($CDCl_3$) δ 7.07 (dd, 1 H, J = 5.73, 9.73 Hz), 6.19 (d, 1 H, J = 9.94 Hz), 3.98 (dd, 1 H, J = 2.55, 5.55 Hz), 3.90 (d, 1 H, J = 2.52 Hz), 3.62 (m, 1 H), 3.50 (m, 1 H), 1.13 (s, 9 H), 0.93 (m, 2 H), 0.00 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 164.3 CO, 143.2 CH, 123.8 CH, 86.7 CH, 67.4 CH, 66.2 CH_2, 34.4 C, 26.6 CH_3, 18.8 CH_2, −1.4 CH_3. R_f = 0.86 (hexane:EtOAc/2:1). HPLC (λ_{max} = 214 nm) de% 97.2%, hexane:2-propanol/95:5, 0.5 mL/min, *anti* 9.66 min, *syn* 14.60 min; ee% 96.5%, hexane:2-propanol 99.5:0.5, 0.5 mL/min, minor 24.80 min, major 32.72 min. Anal. Calcd for $C_{14}H_{26}O_3Si$: C 62.18, H 9.69. Found: C 61.81, H 9.75.

14b (75% yield): $[\alpha]^{21}_D = -288.9°$ (*c* 1.3, $CHCl_3$); IR ($CHCl_3$) 3020, 2958, 2877, 1714, 1262. ^{1}H NMR ($CDCl_3$) δ 7.06 (dd, 1 H, J = 5.71, 9.74 Hz), 6.19 (d, 1 H, J = 9.78 Hz), 3.91 (dd, 1 H, J = 2.66, 5.55 Hz), 3.84 (dd, 1 H, J = 2.62, 9.72 Hz), 3.67 (m, 1 H), 3.50 (m, 1 H), 2.26 (m, 1 H), 1.12 (d, 3 H, J = 6.61 Hz), 0.97 (d, 3 H, J = 6.75 Hz), 0.91 (t, 2 H, J = 8.06 Hz), 0.00 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 163.7 CO, 143.1 CH, 124.1 CH, 85.8 CH, 66.2 CH, 66.1 CH_2, 28.3 CH, 20.0 CH_3, 18.6 CH_2, 18.3 CH_3, −1.4 CH_3. R_f = 0.81 (hexane:EtOAc/2:1). HPLC (λ_{max} = 214 nm) de% 99.3%, hexane:2-propanol 95:5, 0.6 mL/min, *anti* 8.08 min, *syn* 14.23 min; ee% 96.6%, hexane:2-propanol 99.5:0.5, 0.6 mL/min, minor 24.21 min, major 28.43 min. Anal. Calcd for $C_{13}H_{24}O_3Si$: C 60.90, H 9.43; found: C 61.15, H 9.41.

14c (73% yield): $[\alpha]^{21}_D = -284.4°$ (*c* 1.7, $CHCl_3$). IR ($CHCl_3$) 3027, 3013, 2955, 2897, 1731. ^{1}H NMR ($CDCl_3$) δ 7.52−7.32 (m, 3 H), 7.06 (dd, 1 H, J = 5.64, 9.69 Hz), 6.21 (d, 1 H, J = 9.75 Hz), 5.45 (d, 1 H, J = 3.23 Hz), 3.99 (dd, 1 H, J = 2.85, 5.55 Hz), 3.32 (m, 1 H), 2.94 (m, 1 H), 0.70 (m, 2 H), −0.04 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 163.5 CO, 143.0 CH, 135.3 C, 128.4 CH, 128.2 CH, 126.9 CH, 123.0 CH, 81.3 CH, 70.2 CH, 68.4 CH_2, 18.3 CH_2, −1.5 CH_3. R_f = 0.67 (hexane:EtOAc/2:1). HPLC (λ_{max} = 216 nm) de% 97.9%, hexane:2-propanol 95:5, 0.6 mL/min, *anti* 8.45 min, *syn* 22.13 min; ee% 98.4%, hexane:2-propanol 99:1, 0.6 mL/min, minor 27.29 min, major 37.18 min. Anal. Calcd for $C_{16}H_{22}O_3Si$: C 66.17, H 7.64. Found: C 66.16, H 7.71.

14d (74% yield): $[\alpha]^{21}_D = -150.6°$ (*c* 1.3, $CHCl_3$). IR ($CHCl_3$) 3020, 2958, 1725, 1630, 1218. ^{1}H NMR ($CDCl_3$) δ 6.92 (dd, 1 H, J = 4.45, 9.73 Hz), 6.10 (d, 1 H, J = 9.70 Hz), 5.93 (m, 1 H), 5.76 (m, 1 H), 4.85 (dd, 1 H, J = 3.89, 7.24 Hz), 4.01 (t, 1 H, J = 4.09 Hz), 3.64 (m, 2 H), 2.13 (m, 2 H), 1.03 (t, 3 H, J = 7.47 Hz), 0.93 (t, 2 H, J = 8.08 Hz), 0.02 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 163.1 CO, 143.9 CH, 138.7 CH, 122.6 CH, 122.4 CH, 80.7 CH, 70.0 CH, 67.4 CH_2, 25.4 CH_2, 18.5 CH_2, 13.0 CH_3, −1.1 CH_3. R_f = 0.62 (hexane:EtOAc/2:1). HPLC (λ_{max} = 214 nm) de% 98.7%, hexane:2-propanol 95:5, 0.6 mL/min, *anti* 8.36 min, *syn* 13.83 min; ee% 96.5%, hexane:2-propanol 99.5:0.5, 0.6 mL/min, minor 36.27 min, major 39.08 min. Anal. Calcd for $C_{14}H_{24}O_3Si$: C 62.64, H 9.01. Found: C 62.49, H 9.01.

14e (70% yield): $[\alpha]^{21}_D = -124.3°$ (*c* 1.0, $CHCl_3$). IR, ^{1}H, ^{13}C NMR spectra and R_f value were identical with **14f**. HPLC (λ_{max} = 210 nm) de% 98.5%, hexane:2-propanol 95:5, 0.6 mL/min, *anti* 8.99 min, *syn* 14.33 min; ee% 96.8%, hexane:2-propanol 99.5:0.5, 0.6 mL/min, minor 26.99 min, major 28.17 min. Anal. Calcd for $C_{12}H_{20}O_3Si$: C 59.96, H 8.39. Found: C 59.99, H 8.35.

14f (70% yield): $[\alpha]^{21}_D = -124.7°$ (*c* 1.0, $CHCl_3$). IR ($CHCl_3$) 3028, 2957, 1727, 1630, 1379, 1251, 1212. ^{1}H NMR ($CDCl_3$) δ 6.91 (dd, 1 H, J = 4.33, 9.90 Hz), 6.09 (m, 2 H), 5.46 (m, 2 H), 4.93 (m, 1 H), 4.10 (t, 1 H, J = 4.33 Hz), 3.63 (m, 2 H), 0.90 (m, 2 H), 0.00 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 163.2 CO, 143.8 CH, 131.7 CH, 122.6 CH, 119.4 CH_2, 80.2 CH, 69.8 CH, 67.5 CH_2, 18.5 CH_2, −1.4 CH_3. R_f = 0.59 (hexane:EtOAc/2:1). HPLC (λ_{max} = 210 nm) de% 98.9%, hexane:2-propanol 95:5, 0.6 mL/min, *anti* 9.59 min, *syn* 14.10 min; ee% 97.7%, hexane:2-propanol 99.5:0.5, 0.6 mL/min, minor 27.62 min, major 29.01 min. HREI: calcd for $C_{12}H_{20}O_3Si$: 240.1182; molecular ion not observed, found: 169.0687 for $(C_8H_{13}O_2Si)^+$, 73.0474 for $(C_3H_9Si)^+$.

(3*R*,4*S*)-5-Keto-4-[β-(trimethylsilyl)ethoxy]-3-vinyloxacyclohexan-2-one (2). To a solution of **12e** (1.5 mmol, 1.1 g) in THF (3 mL) was added HCl (2.5 mL of 3 N aqueous solution, 7.5 mmol) dropwise. Stirring was continued for 3−5 h until the starting material could not be detected from TLC. The mixture was extracted twice with EtOAc. The combined organic layers were washed with water, dried over Na_2SO_4, and concentrated. The crude yellowed oil was chromatographed (hexane:EtOAc/1.5:1) to yield the β-keto lactone **2** (299 mg, 78% yield) as a pale yellow oil. $[\alpha]^{21}_D = -44.2°$ (*c* 1.2, $CHCl_3$); IR ($CHCl_3$) 3019, 2956, 1740, 1359, 1125. ^{1}H NMR ($CHCl_3$) δ 5.99 (m, 1 H), 5.45 (m, 2 H), 5.05 (m, 1 H), 4.08 (d, 1 H, J = 4.15 Hz), 3.86 (m, 1 H), 3.63 (m, 1 H), 3.47 (m, 2 H), 0.99 (t, 2 H, J = 8.29 Hz), 0.02 (s, 9 H). ^{13}C NMR ($CHCl_3$) δ 192.3 CO, 167.5 CO, 131.0 CH, 119.7 CH_2, 79.7 CH, 77.2 CH, 69.6 CH_2, 44.2 CH_2, 18.2 CH_2, −1.4 CH_3. R_f = 0.23 (hexane:EtOAc 1:1.85). HRMS: calcd 256.1311 for $C_{12}H_{20}O_4Si$, molecular ion not observed, found: 255.1052 for $(M - H)^+$, 73.0471 for $(C_3H_9Si)^+$.

(3*R*,4*S*,5*R*)-5-hydroxy-4-[β-(trimethylsilyl)ethoxy]-3-vinyloxacyclohexan-2-one (16). A solution of β-keto lactone **2** (1.0 mmol, 0.26 g), cerium(III) chloride heptahydrate (1.0 mmol, 0.37 g) in methanol (4.0 mmol, 0.16 mL), and THF (2.5 mL) was cooled to 0 °C and stirred for 10 min. Sodium borohydride (1.1 mmol, 42 mg) was added in one portion. The reaction was continued for 30 min at 0 °C and then quenched with water. The mixture was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to afford crude **15** as a yellow oil. To a solution of crude **15** in benzene (10 mL) was added silver carbonate on Celite [3.0 mmol, 1.65 g (contains 50 wt % Ag_2CO_3)]. The mixture was refluxed for 5−8 h. After the reaction was completed, the mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was concentrated. The crude brown oil was chromatographed to yield the β-hydroxy lactone **16** (0.21 g, 80% yield) as a pale yellow oil. $[\alpha]^{21}_D = +75.0°$ (*c* 1.3, $CHCl_3$). IR ($CHCl_3$) 3566, 3020, 2956, 2360, 1739, 1681, 1583. ^{1}H NMR ($CDCl_3$) δ 6.00 (m, 1 H), 5.72 (m, 2 H), 4.68 (dd, 1 H, J = 0.74, 5.52 Hz), 4.13 (m, 1 H), 3.80 (m, 1 H), 3.73 (m, 2 H), 2.85 (dd, 1 H, J = 6.63, 17.58 Hz), 2.70 (dd, 1 H, J = 9.58, 17.58 Hz), 2.48 (d, 1 H, J = 8.6 Hz), 0.96 (t, 2 H, J = 8.38 Hz), 0.01 (s, 9 H). ^{13}C NMR ($CDCl_3$) δ 169.3 CO, 132.9 CH, 132.5 CH_2, 80.2 CH, 76.6 CH, 71.1 CH_2, 66.2 CH, 35.6 CH_2, 18.8 CH_2, −1.5 CH_3. R_f = 0.45 (hexane:EtOAc/1:1). HREI: calcd 258.1287 for $C_{12}H_{22}O_4Si$, molecular ion not observed, found: 173.0639 for $(C_7H_{13}O_3Si)^+$, 169.0687 for $(C_8H_{13}O_2Si)^+$, 101.0784 for $(C_5H_{13}Si)^+$, 73.0474 for $(C_3H_9Si)^+$.

Lactone 17. β-Hydroxy lactone **16** (0.80 mmol, 206 mg) was dissolved under nitrogen in dichloromethane (2 mL) at 0 °C, boron trifluoride etherate (1.6 mmol, 0.2 mL) was added, and the mixture was stirred at 0 °C for 30 min and at room temperature for 2 h. The volatiles were removed at ca. 5 Torr. The residue was dissolved in DMF (1 mL) and acetone (0.2 mL), stirred with a catalytic amount of PPTS at room temperature, and 2,2-dimethoxypropane (5.0 mmol, 0.61 mL) was added and stirred for 12 h. Additional 2,2-dimethoxypropane (2.5 mmol, 0.31 mL) was added and stirred for another 12 h. The mixture was then concentrated under reduced pressure. The crude yellow oil was chromatographed (hexane:EtOAc/1.5:1) to yield lactone **17** (154 mg, 78% yield) as a colorless oil. $[\alpha]^{21}_D = +48.8°$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3020, 2995, 1759, 1455. ^{1}H NMR ($CDCl_3$) δ 6.01 (m, 1 H), 6.45 (m, 2 H), 4.75 (m, 1 H), 4.57 (d, 1 H, J = 6.30 Hz), 4.45 (dd, 1 H, J = 1.69, 7.71 Hz), 2.92 (dd, 1 H, J = 2.07, 15.91 Hz), 2.55 (dd, 1 H, J = 3.62, 15.91 Hz), 1.47 (s, 3 H), 1.35 (s, 3 H). ^{13}C NMR

($CDCl_3$) δ 169.0 CO, 131.2 CH, 119.3 CH_2, 78.6 CH, 74.5 CH, 71.4 CH, 25.9 CH_3, 24.1 CH_3. $R_f = 0.73$ (hexane:EtOAc/1:1). Anal. Calcd for $C_{10}H_{14}O_4$: C 60.60, H 7.12; found: C 60.41, H 7.16.

Lactone 19. Osmium tetraoxide (0.052 mmol, 42 μL of 2.5 wt % solution in *tert*-butyl alcohol) was added to a solution of *N*-methylmorpholine *N*-oxide (0.72 mmol, 84 mg), water (2 mL), and acetone (0.4 mL) in THF (0.7 mL). After 10 min, the olefin **17** (0.65 mmol, 129 mg) in acetone (0.2 mL) and THF (0.2 mL) was added dropwise. The reaction was completed after stirring overnight at room temperature. A slurry mixture of sodium bisulfite (50 mg) and magnesol (100 mg) in water (0.5 mL) was added and stirred for 10 min, and the solid was then filtered. The filtrate was adjust to pH 2 with 1 N H_2SO_4. The solution was saturated with NaCl and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried and concentrated to yield the crude diol **18** as a white foam. The material was dissolved in DMF (0.8 mL) and acetone (0.17 mL), stirred with catalytic amount of PPTS at room temperature, and 2,2-dimethoxypropane (4.0 mmol, 0.49 mL) was added and stirred overnight. A second portion of 2,2-dimethoxypropane (2.0 mmol, 0.25 mL) was added and stirred for another 12 h. The mixture was concentrated under vacuum. The residue was chromatographed (hexane:EtOAc/1.5:1) to provide lactone **19** (0.16 g, 90% yield) as a white solid. $[\alpha]^{21}_D = +65.1°$ (*c* 1.2, $CHCl_3$). mp 116−118 °C. IR ($CHCl_3$) 2992, 2936, 1762, 1455. ^{1}H NMR ($CDCl_3$) δ 4.72 (m, 1 H), 4.56 (dd, 1 H, $J = 1.17$, 7.93 Hz), 4.35 (m, 1 H), 4.05 (m, 2 H), 3.91 (dd, 1 H, $J = 1.05$, 8.63 Hz), 2.83 (dd, 1 H, $J = 1.99$, 15.88 Hz), 2.51 (dd, 1 H, $J = 3.38$, 15.95 Hz), 1.40 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H), 1.32 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 168.8 CO, 109.7 C, 109.6 C, 77.7 CH, 72.7 CH, 71.3 CH, 71.2 CH, 66.6 CH_2, 34.6 CH_2, 27.0 CH_3, 25.8 CH_3, 25.0 CH_3, 24.1 CH_3. $R_f = 0.62$ (hexane:EtOAc/1:1). Anal. Calcd for $C_{13}H_{20}O_6$: C 57.34, H 7.39. Found: C 57.16, H 7.45.

Ester 20. *tert*-Butyllithium (0.61 mmol, 0.36 mL of 1.7 M solution in pentane) was added dropwise to a solution of ethyl vinyl ether (0.97 mmol, 92 μL) in dry THF (1 mL) at −65 °C under nitrogen. After removal of the cooling bath the yellow precipitate redissolved and the solution became colorless between −5 °C to 0 °C. The solution was recooled to −78 °C. A solution of lactone **19** (0.55 mmol, 0.15 g) in THF (0.5 mL) was added. The stirring was continued for 30 min at −78 °C and then quenched with saturated NH_4Cl aqueous solution. The mixture was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried and the solvent removed to yield a pale yellow oil. The material was dissolved in CH_2Cl_2 (2.5 mL) and cooled to −60 °C, methanol (0.3 mL) was added, and the cold mixture was ozonolyzed. After excess of ozone was removed by N_2 stream, 2 equiv of dimethyl sulfide was added. This mixture was warmed to 0 °C for 20 min and then concentrated under vacuum to yield the crude product as a pale yellow oil. This residue was chromatographed to provide the KDO derivative **20** (0.164 g, 86% yield) as a colorless oil. $[\alpha]^{21}_D = +29.1°$ (*c* 1.6, $CHCl_3$). IR ($CHCl_3$) 3524, 2990, 2937, 1737, 1455. ^{1}H NMR ($CDCl_3$) δ 4.49 (m, 1 H), 4.37−4.21 (m, 4 H), 4.09−3.97 (m, 2 H), 3.91−3.86 (m, 1 H), 2.49 (dd, 1 H, $J = 6.48$, 14.47 Hz), 1.88 (dd, 1 H, $J = 4.77$, 14.46 Hz), 1.45 (s, 3 H), 1.41 (s, 3 H), 1.36 (s, 3 H), 1.34 (s, 3 H), 1.30 (t, 3 H, $J = 7.3$ Hz). ^{13}C NMR ($CDCl_3$) δ 169.6 CO, 109.3 C, 109.1 C, 94.3 C, 73.9 CH, 71.3 CH, 70.5 CH, 69.9 CH, 66.8 CH_2, 62.2 CH_2, 32.3 CH_2, 27.0 CH_3, 26.8 CH_3, 25.6 CH_3, 25.3 CH_3, 14.0 CH_3. $R_f = 0.43$ (hexane:EtOAc/2:1). Anal. Calcd for $C_{16}H_{26}O_8$: C 55.48, H 7.56. Found: C 55.27, H 7.49.

(+)-KDO Ammomiun Salt (21). A solution of ester **20** (3.81 mmol, 132 mg) in 90% HOAc (12 mL) was heated to 90 °C for 45 min. The solution was cooled to ambient temperature and then concentrated under vacuum at a temperature not exceeding 50 °C. To the solution of the residue in water (1 mL) was added NaOH (7 mL of 0.1 N aqueous solution). The solution was stirred at room temperature for 2 h and then acidified with Dowex-50W-X4 (20−50 mesh) to pH 3, and the resin was removed by filtration. The filtrate was concentrated to yield the crude free KDO, **1**, as a white solid. This crude KDO was dissolved in water (1 mL), and concentrated aqueous NH_3 was added until pH 11. The solution was stirred for 30 min at room temperature and concentrated under vacuum at a temperature not exceeding 50 °C to yield the crude KDO ammonium salt as a white solid. Recrystallization from 90% aqueous ethanol provided the pure KDO ammonium salt (92.5 mg, 89% yield) as a white, fluffy solid. mp 123−126 °C. $[\alpha]^{21}_D = +39.5°$ (*c* 1.2, H_2O); authentic sample from Sigma Co.: mp 122−125 °C, $[\alpha]^{21}_D = +40.9°$ (*c* 0.9, H_2O). The synthetic sample has an identical NMR spectrum and TLC behavior with the authentic sample: ^{1}H NMR (D_2O) δ 4.48−4.35 (m), 4.11−3.94 (m), 3.80−3.70 (m), 3.61−3.52 (m), 2.52 (dd, $J = 6.92$, 14.14 Hz), 2.31 (m), 2.03−1.79 (m). ^{13}C NMR (D_2O) δ 176.7 CO, 96.4 C, 71.1 CH, 69.2 CH, 66.6 CH, 66.2 CH, 62.9 CH_2, 33.6 CH_2. $R_f = 0.56$ (MeOH:$CHCl_3$:H_2O/10:10:3). Anal. Calcd for $C_8H_{17}NO_8$: C 35.17, H 7.00, N 5.13; found: C 35.34, H 6.90, N 5.09.

Compound 22. The synthetic KDO ammonium salt **21** (45 mg, 0.165 mmol) was peracetylated and esterificated with diazomethane according to the literature procedure to afford methyl ester **22** (61 mg, 80% yield) as a colorless oil. $[\alpha]^{21}_D = +99.7°$ (*c* 1.2, MeOH). IR ($CHCl_3$) 2956, 1747, 1370. ^{1}H NMR ($CDCl_3$) δ 5.38 (m, 1 H), 5.31 (m, 1 H), 5.21 (m, 1 H), 4.46 (dd, 1 H, $J = 2.09$, 12.25 Hz), 4.19−4.08 (m, 2 H), 3.80 (s, 3 H), 2.23−2.17 (m, 2 H), 2.13 (s, 3 H), 2.10 (s, 3 H), 5.19 (s, 6 H), 4.49 (s, 3 H). ^{13}C NMR ($CDCl_3$) δ 170.4 CO, 170.2 CO, 169.9 CO, 169.5 CO, 167.9 CO, 166.6 CO, 97.4 C, 69.7 CH, 67.3 CH, 65.9 CH, 63.9 CH, 62.0 CH_2, 53.1 CH_3, 30.9 CH_2, 20.7 CH_3, 20.6 CH_3. $R_f = 0.51$ (hexane:EtOAc/1:1). Anal. Calcd for $C_{19}H_{26}O_{13}$: C 49.35, H 5.66; found: C 49.54, H 5.71.

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