Formal Synthesis of 3-Deoxy-D-manno-2-Octulosonic Acid (KDO) via a Highly Double-Stereoselective Hetero Diels−Alder Reaction Directed by a (Salen)Co^{II} Catalyst and Chiral Diene

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This paper presents a formal total synthesis of 3-deoxy-D-manno-2-octulosonic acid (KDO) based on a highly double-stereoselective hetero Diels−Alder reaction between an electron-rich diene and ethyl glyoxylate catalyzed by (Salen)Co^{II} complex, a new catalyst for Diels−Alder reactions. A facial specific hydroboration followed by oxidative workup leads to a diol system with the trans-diequatorial arrangement of hydroxyl groups at the C-4 and C-5. Inversion of the configuration of the C-5 hydroxyl group in **12** and then ketal formation afford the desired target diisopropylidene-2-deoxy-KDO methyl ester (**18**), which can be converted to KDO according to the literature procedure.

The monosaccharide 3-deoxy-D-*manno*-2-octulosonic acid (KDO) is an essential constituent of the outer membrane lipopolysaccharide (LPS) of Gram-negative bacteria. It has been shown[1] that the incorporation of KDO is highly likely to be a vital step in the growth of Gram-negative bacteria. For this reason KDO is chosen by many workers as a lead in developing rationally designed inhibitors for the cell-wall assembly process. As a consequence of this trend, work toward the synthesis of KDO and its analogues has accelerated, and several such endeavors, including enzymatic syntheses,[2] semi-syntheses starting from carbohydrates,[3a−c] and *de novo* syntheses,[4] have already appeared in the literature.

We were attracted to this area by the work of Lubineau[3b] et al., in which a hetero cycloaddition of chiral dienes to glyoxylate was employed as the key step for the construction of both 2-deoxy KDO and KDO. While the value of Lubineau's original protocol (as well as the modified one) as a novel methodology for construction of highly substituted tetra- or dihydropyrans is unequivocal, the low (*endo*/*exo*, *re*/*si*) selectivities[5,6] and the poor yields of the cycloaddition reaction obviously thwart any possible synthetic applications. This prompted us to initiate the work disclosed below.

We began our explorations with examining electron-deficient dienes. The initial experiments with a 2-phenylsulfonyl 1,3-diene were rather disappointing, for (with or without Lewis acid catalysts) no reactions occurred at all at room temperature. Later, it was found that the expected reaction could take place at higher temperatures. However, the low selectivities suggested that the phenylsulfonyl was not a good activating group.[7] This result turned our attention to the electron-rich 2-silyloxy dienes.

The needed silyloxy diene (**6**,[8a] Scheme 1) was prepared from enones **3** and **4**[8b] (obtained as a 1:3 mixture from the Wittig reaction between *O*-isopropylidene-D-glyceraldehyde[8c] and acetonylidenetriphenylphosphorane) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (triflate).[9] The TMS (trimethylsilyl) counterpart of **6** could also be used, although it was less stable and much less reactive than **6**. The diene **6** was then treated with ethyl glyoxylate (freshly distilled). After 4 hours of reaction at 40 °C, all four possible adducts (**8a**−**d**) were produced

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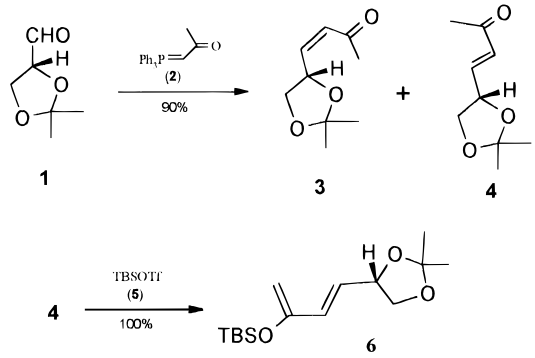
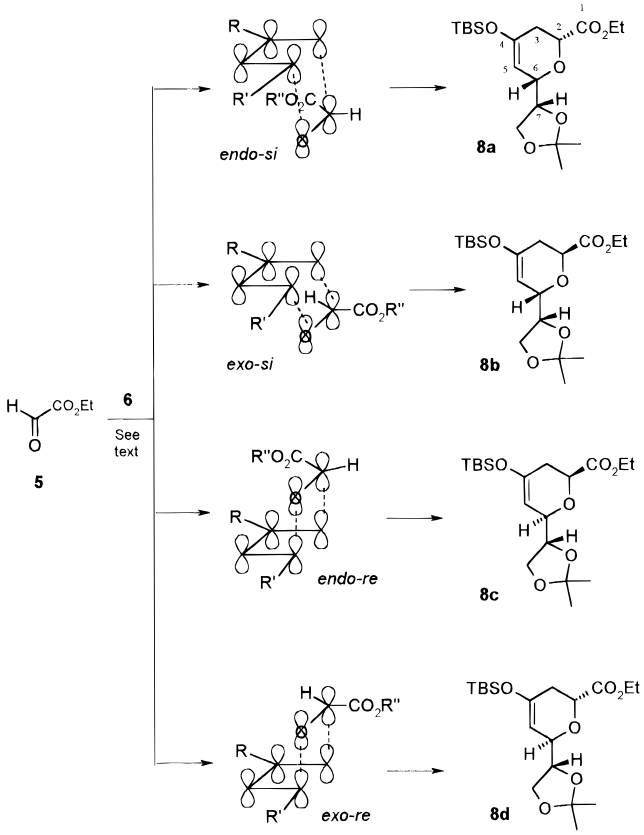
Scheme 1



Scheme 2



(Scheme 2) in 90% total yield. These isomers were then separated on silica gel and characterized separately (except **8d**, which could not be obtained in high purity).

To facilitate the assignment of the stereochemistries of C2 and C6, the major components **8a** and **8c** were converted to corresponding diacetates **9a** and **9c** (Scheme 3) and subjected to intensive ^{1}H NMR analyses. The $^3J_{2,3}$ values for both **9a** and **9c** were found to be 2.4 and 12.3 Hz, which were consistent with the known rule that in cyclohexane systems $^3J_{a,e}$ should be significantly smaller than $^3J_{a,a}$ (If the H were in an equatorial position, the two *J*'s would be the same because $^3J_{e,e} \approx {}^3J_{a,e}$). Therefore, the orientation of the H at C2 is assigned to axial (which means that these adducts were formed through an *endo* transition state).

The stereochemistry of C6 was established according to the empirical rules in the literature,[10] i.e., the KDO type of configuration has a "large" $^3J_{6,7}$ (6−7 Hz) whereas the KDN or sialic acid type of configuration has a "small" $^3J_{6,7}$ (0−3.5 Hz). Since the observed $^3J_{6,7}$'s for **9a** and **9c**

Scheme 3

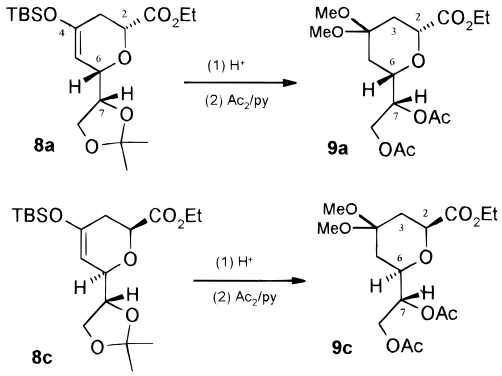


Table 1. Results of Cycloaddition of Diene 6 to Ethyl Glyoxylate in CH_2Cl_2

entry	catalyst	temp (°C)	yield (%)	**8a**:**8b**:**8c**:**8d**	*endo/exo*	*si/re*
1	none	60	90	35:20:21:24	56/44	55/45
2	none	20	50	40:16:23:21	63/37	56/44
3	none	0	30	56:11:20:13	76/24	67/33
4	$ZnCl_2$	−78	60	45:15:23:17	68/32	60/40
5	Et_2AlCl[a]	−78	65	45:15:26:14	71/29	60/40
6	**10**	−78	75	22:11:44:23	66/34	33/67
7	**11**	40	90	65:12:21:2	86/14	77/23
8	**11**	20	85	80:5:13:2	93/7	85/15
9	**11**	0	50[b]	77:4:14:5	91/9	81/19

[a] Strong Lewis acids such as $AlCl_3$ and $BF_3{\cdot}OEt_2$ decompose **6** and therefore cannot be used here. [b] When the reaction temperature was below −30 °C, lower yields were obtained even after prolonged reaction.

were 6.7 and 3.8 Hz, respectively, the absolute configurations at the C6 were assigned to *S* for **9a** (and consequently **8a**) and *R* for **9c** (and consequently **8c**). Further evidence for the stereochemistries of the major isomers **9a** and **9c** was obtained from the phase-sensitive NOESY experiments, which showed significant cross-peaks correlating the H2, H5, and H6.[10] With the stereochemistries of **8a** and **8c** established, the remaining two isomers (**8b** and **8d**) were also easily assigned by analogy.

Having found a satisfactory diene and established the essential means to identify the product isomers, we were now in a position to deal with the selectivity problem. We first examined the temperature effect. It appeared (Table 1) that with the increase of the reaction temperature, the yield increased significantly but the selectivities became even poorer, implying the necessity of using a catalyst. We then tested a few common Lewis acids. The strong acids such as $BF_3{\cdot}OEt_2$ and $AlCl_3$ led to decomposition of **6** and therefore were not suitable for our purpose. $ZnCl_2$ and Et_2AlCl speeded up the reaction dramatically. However, the selectivities were still rather poor. It seemed to us at this point that only the chiral induction from the substrate was not enough. Therefore we tried next the chiral vanadium catalyst **10**[11] (Scheme 4). The result was somewhat to our surprise; besides the expected rate acceleration, the *re/si* selectivity was reversed. This was later attributed to the mismatched chiral induction effect of the catalyst (which worked against that of the substrate, see below), so that the

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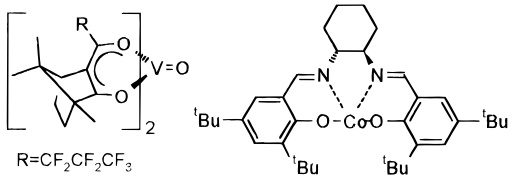
Scheme 4



10 **11**

attack of the dienophile occurred mainly on the *re* face of the diene, giving **8c** and **8d**.

Salen-derived compounds[12,13] have found wide applications in many types of asymmetric reactions (but not Diels−Alder reactions) in recent years. Enlightened by these successful cases, we tested the (Salen)Co^{II} complex (**11**)[14] in our reaction. We were pleased to find that with this compound as catalyst the cycloaddition reaction underwent easily and exhibited good double diastereoselectivity. At 40 °C, the total yield was as high as 90% although the *endo*/*exo* and *si*/*re* selectivities were only 86/14 and 77/23, respectively (Table 1). The selectivities were remarkably improved (*endo*/*exo* = 93/7, *si*/*re* = 85/15) when the reaction temperature was lowered to 20 °C. Further decreasing the temperature, however, was not rewarding; the yield was significantly reduced but the selectivities were not getting any better.

In contrast to the situation with catalyst **10**, the asymmetric induction effect of the **11** seems to be matched with that of the substrate so that one of the isomers, **8a**, predominated over others. This compound has the same stereochemistry at C6 as KDO's and therefore could be very useful as a precursor to KDO type of compounds.

In the present work, further elaboration of **8a** was done as shown in Scheme 5, starting with introducing a hydroxyl group at the C5 by hydroboration. Due to the steric hindrance[15] caused by the substituent at C6, the OH "entered" from the wrong direction. An inversion of configuration at C5 thus became unavoidable. We first tried Mitsunobu reaction. Unfortunately, this did not work out. So we had to take a round-about way to oxidize[16] **12** into **14**, followed by reducing it to **13** with a proper reducing agent. To our delight, after failure with BH_3 (with which no reactions occurred, even under forcing conditions) and L-Selectride (giving rather complicated products) the desired **13** could be obtained as the sole product by reduction at −15 °C with $NaBH_4$/$CeCl_3$ in ethanol. At higher temperature (0 °C), the ester group was also reduced.

Exposure of the intermediate **13** to acidic ion-exchange resin Amberlyst 15 in methanol at 40 °C removed both the TBS and isopropylidene protecting groups in **13**. After masking the diols as diacetonides with 2,2-dimethoxypropane, **17** and **18**[17] (formed via ester exchange) were obtained, which could be converted to KDO by the literature procedure.[3,18]

Summary

In the preceding paragraphs we present a successful hetero Diels−Alder reaction between an electron-rich diene and ethyl glyoxylate, where with the (Salen)Co^{II} complex **11** as catalyst (which has not been tested for Diels−Alder and hetero Diels−Alder reactions before) good selectivities (*endo*/*exo* = 93/7, *si*/*re* = 85/15) were achieved. The major product **8a** was further elaborated into diisopropylidene-2-deoxy-KDO methyl ester **18** and thus completed a formal total synthesis of KDO.

Experimental Section

General. Melting points (mp) were uncorrected. IR spectra were recorded on a Shimadzu IR-440 spectrometer. ^1H and ^{13}C NMR were recorded on EM-360A, FX 90q, AMX-300, or AMX-600 spectrometers with TMS as an internal standard. Mass spectra were taken on VG Quattro MS/MS, HP5989A, Finnigan Mat 8430 instruments. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. Flash column chromatography was performed on silica gel H (10−40 μm) and with petroleum ether−ethyl acetate system as eluant. Microanalyses were carried out in the Microanalytical Laboratory at Shanghai Institute of Organic Chemistry.

(4*S*)-(*Z*)-4,5-(Isopropylidenedioxy)hexa-3-en-2-one (3) and (4*S*)-(*E*)-4,5-(Isopropylidenedioxy)hexa-3-en-2-one (4).[8b] To a solution of *O*-isopropylidene-D-glyceraldehyde (1.3 g, 10 mmol, freshly prepared from 1,2:5,6-di-*O*-isopropylidene-D-mannitol) in 150 mL of THF was added 3.82 g (12 mmol) of acetonylidenetriphenylphosphorane. This solution was refluxed for 2 h. After cooling, the reaction mixture was passed

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(14) [(*R*,*R*)-*N*,*N*′-Bis(3,5-di-*tert*-butylsalicyclidene)-1,2-cyclohexanediaminato(2−)]cobalt (**11**) was prepared as follows: NaOH (95%, 421 mg) in anhydrous EtOH (25 mL) was added to a mixture of the ligand (2.73 g, 5 mmol, 1.0 equiv) in ethanol (25 mL). After completion of the addition, the mixture was heated to reflux with stirring for ca. 30 min until the suspension became a solution. $CoCl_2 \cdot 6H_2O$ (1.20 g, 5 mmol, 1 equiv) in anhydrous ethanol (25 mL) was then added over 45 min. The addition funnel was rinsed with ethanol (3 mL), and the stirring was continued at reflux for 4 h. The reaction was monitored by TLC (EtOAc/petroleum ether 1:4; free ligand $R_f = 0.95$; **11** $R_f = 0.10$. EtOAc/hexane 1:2; **11** $R_f = 0.50$) until no free ligand was left. The mixture (a dark yellow solution over a thick, medium brown oily layer) was allowed to cool to room temperature. The precipitated brown solid was collected by suction filtration and then dried under high vacuum at 50−60 °C for 1 h to yield the desired catalyst **11** (a brown, water-soluble powder, 2.76 g, 92%) as an orange crystal: mp >330 °C. $[\alpha]^{20}_D$ −1100 (*c*, 0.01, CH_2Cl_2). IR (neat): 2951, 1610, 1595, 1527, 1360, 1254, 1176, 787, 758, 543 cm^{-1}. EIMS (*m*/*z*): 603 (M^+, 100.00), 588 (63.66), 516 (5.17), 286 (36.86), 276 (5.92), 260 (5.08), 258 (6.52), 242 (2.42), 57 (3.88). HREIMS calcd for $C_{36}H_{52}N_2O_2Co$ 603.3361. Found 603.3354. Preparative scale isolation of **11** was most conveniently achieved by crystallization from ethanol. We finished the above preparation two years ago. After we had sent in the first version of this manuscript, we noticed Leung's report on the X-ray crystal structure of (*R*,*R*)-Salen(Co): Leung, W.-H.; Chan, E. Y.; Chow, E. K. F.; Williams, I. D.; Peng, S.-M. *J. Chem. Soc., Dalton Trans.* **1996**, 1229. More recently, Jacobsen also reported on the use of (*S*,*S*)-Salen(Co), the enantiomer of **11**, in enantioselective catalytic ring-opening of epoxides by carboxylic acids: Jacobsen, E. J.; Kakiuchi, F.; Konsler, R.; Larrow, J. F.; Tokunaga, M. *Tetrahedron Lett.* **1997**, *38*, 773.

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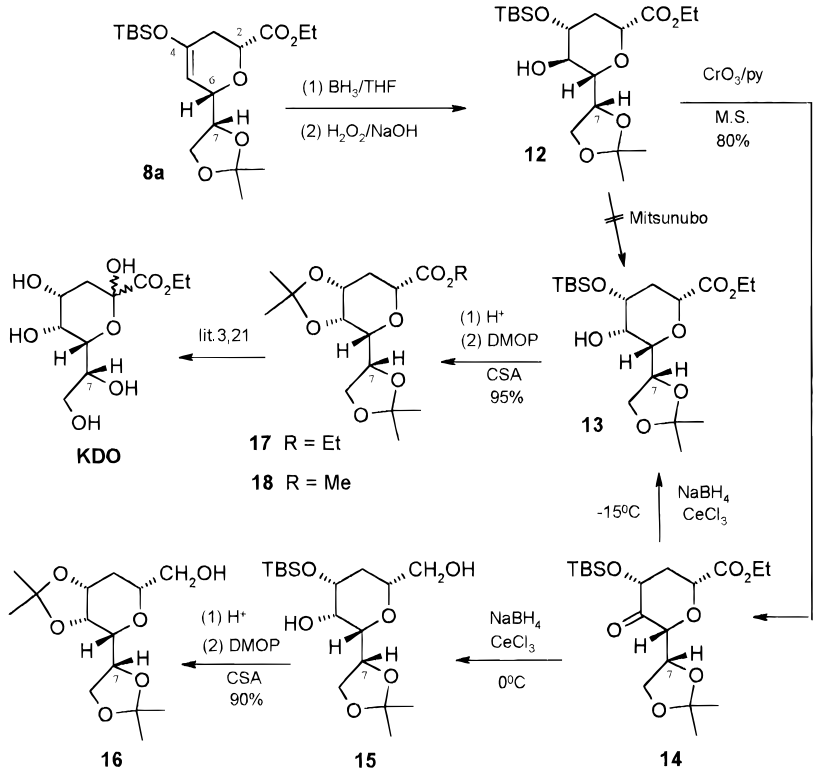
Scheme 5



through a short pad of silica gel (10% ethyl acetate−petroleum as eluant) to remove the triphenylphosphine oxide. The filtrate was concentrated and subjected to flash chromatography eluted with 10% ethyl acetate−petroleum ether to give 1.21 g (7.1 mmol, 71%) of **4** and 0.40 g (2.4 mmol, 24%) of **3** as a clear oil. Compound **3**: TLC: $R_f = 0.32$. $[\alpha]^{20}_D$ +188.3 (*c*, 3.7, $CHCl_3$). IR (neat): 2988, 2939, 1695, 1616, 1406, 1381, 1258, 1215, 1162, 1057, 858 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 6.27 (1 H, d, $J = 2.1$ Hz), 6.38 (1 H, dt, $J = 6.9, 2.1$ Hz), 4.46 (1 H, t, $J = 7.8$ Hz), 4.10 (1 H, m), 3.60 (1 H, t, $J = 7.8$ Hz), 2.26 (3 H, s), 1.49 (3 H, s), 1.42 (3 H, s).

Compound **4**: $R_f = 0.30$. $[\alpha]^{20}_D$ +42.7 (*c*, 3.8, $CHCl_3$). (lit.[8b] $[\alpha]^{25}_D$ +49.5). IR (neat): 2988, 1687, 1373, 1258, 1221, 1178, 1061, 939, 660 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 6.82 (1 H, dd, $J = 16.8, 5.7$ Hz), 6.26 (1 H, d, $J = 16.8$ Hz), 6.64 (1 H, m), 4.16 (1 H, t, $J = 7.5$ Hz), 3.68 (1 H, t, $J = 7.5$ Hz), 2.24 (3 H, s), 1.44 (3 H, s), 1.42 (3 H, s).

(1′*E*,4*S*)-4-[3′-(*tert*-Butyldimethylsilyloxy)buta-1′,3′-dienyl]-2,2-dimethyl-1,3-dioxolane (6).[8a] To an ice-cooled solution of **4** (1.10 g, 6.5 mmol) in ether (20 mL) were added dropwise 1.41 g (10.2 mmol) of triethylamine and 2.23 g (8.44 mmol) of *tert*-butyldimethylsilyl triflate. After stirring for 5 min, the cooling bath was removed, and the two-phase mixture was stirred at 0 °C for 15 min and then at 20 °C for 1 h. The mixture was concentrated and passed through a pad of silica gel (petroleum ether as the eluant) to give 1.85 g (6.5 mmol, 100%) of **6**[8a] as a thick, yellow oil: $R_f = 0.20$. $[\alpha]^{20}_D$ +17.0 (*c*, 1.2, CH_2Cl_2). ^1H NMR (90 MHz, $CDCl_3$): δ 6.12 (1 H, d, $J =$ 15.2 Hz), 5.92 (1 H, dd, $J = 15.2, 7.1$ Hz), 4.56 (1 H, q, $J = 7.1$ Hz), 4.31 (2 H, s), 4.09 (1 H, dd, $J = 8.5, 6.3$ Hz), 3.58 (1 H, t, $J = 8.0$ Hz), 1.42 (3 H, s), 1.38 (3 H, s).

Ethyl 2,5-Dideoxy-4-*O*-(*tert*-butyldimethylsilyl)-6,7-*O*-isopropyliden-4-ene-D-*ribo*- and -D-*arabino*-octonate (8a and 8c). Thermal Diels−Alder Reactions. A mixture of diene **6** (2.84 mg, 1.0 mmol) and ethyl glyoxylate (112 mg, 1.1 mmol) was heated at 60 °C in an autoclave for 4 h. The reaction mixture was cooled and passed through a silica gel column by using 5% ethyl acetate−petroleum as the eluant to give **8a**, **8b**, and **8c** in 90% yield as colorless oil (pure **8d** could not be obtained). Compound **8a**: $R_f = 0.30$. $[\alpha]^{20}_D$ +42.0 (*c*, 1.58, $CHCl_3$). IR (neat) 2980, 1743, 1374, 1194, 1103, 815, 640 cm^{-1}. ^1H NMR (600 MHz, CD_3COCD_3): δ 5.12 (1 H, t, $J =$ 1.6 Hz, H-5), 4.28 (1 H, dd, $J = 10.9, 3.8$ Hz, H-2), 4.19 (2 H, q, $J = 7.1$ Hz, OCH_2CH_3), 4.16 (1 H, m, H-7), 4.02 (1 H, dd, $J =$ 8.1, 6.1 Hz, H-8), 3.94 (1 H, dd, $J = 8.1, 5.2$ Hz, H-8), 3.92 (1 H, m, H-6), 2.35 (1 H, m), 2.21 (1 H, m), 1.38 (3 H, s), 1.29 (3 H, s), 1.26 (3 H, t, $J = 7.1$ Hz, OCH_2CH_3), 0.94 (9 H, s), 0.20 (6 H, s). ESIMS (*m*/*z*): 409 (M^+ + Na) 387 (M^+ + 1), 369, 329, 311, 255, 237, 197, 179, 149, 73. Anal. Calcd for $C_{19}H_{34}O_6Si$: C, 59.04; H, 8.87. Found: C, 59.06; H, 9.01. Compound **8b**: $R_f = 0.29$. $[\alpha]^{20}_D$ +20.0 (*c*, 1.93, $CHCl_3$). IR (neat): 2960, 1745, 1372, 1226, 1195, 1149, 1102, 1050, 813, 602 cm^{-1}. ^1H NMR (600 MHz, CD_3COCD_3): δ 4.81 (1 H, m, H-5), 4.63 (1 H, dd, $J = 6.0, 3.9$ Hz, H-2), 4.56 (1 H, m, H-6), 4.17 (2 H, q, $J = 7.1$ Hz), 4.13−4.19 (1 H, m, H-7) 3.94 (1 H, dd, $J = 8.2, 6.7$ Hz, H-8), 3.75 (1 H, dd, $J = 8.2, 6.5$ Hz, H-8), 2.44 (1 H, m, H-3), 2.35 (1 H, m, H-3), 1.34 (3 H, s), 1.29 (3 H, s), 1.23 (3 H, t, $J = 7.1$ Hz), 0.92 (9 H, s), 0.172 (3 H, s), 0.168 (3 H, s). EIMS (*m*/*z*): 317 (37.4), 299 (7.2), 2.89 (13.3), 257 (18.2), 225 (19.9), 203 (43.3), 197 (49.8), 183 (26.1), 175 (43.6), 165 (89.2), 143 (31.1), 117 (100.0), 43 (97.7). Anal. Calcd for $C_{19}H_{34}O_6Si$: C, 59.04; H, 8.87. Found: C, 59.03; H, 9.00. Compound **8c**: $R_f = 0.28$. $[\alpha]^{20}_D$ −21.1 (*c*, 1.33, $CHCl_3$). IR (neat): 2961, 1745, 1437, 1121, 1195, 1102, 947, 775 cm^{-1}. ^1H NMR (600 MHz, CD_3COCD_3): δ 4.86 (1 H, t, $J = 1.7$ Hz, H-5), 4.38 (1 H, m, H-7), 4.26 (1 H, dd, $J = 11.0, 3.7$ Hz, H-2), 4.22 (1 H, dd, $J = 11.6, 5.7$ Hz, H-6), 4.17 (2 H, q, $J = 7.1$ Hz), 3.95 (1 H, dd, $J = 8.4, 7.0$ Hz, H-8), 3.73 (1 H, dd, $J = 8.4, 5.9$ Hz, H-8), 2.33 (1 H, m, H-3), 2.19 (1 H, m, H-3), 1.38 (3 H, s), 1.28 (3 H, s), 1.23 (3 H, t, $J = 7.1$ Hz), 0.92 (9 H, s), 0.19 (3 H, s), 0.18 (3 H, s). EIMS (*m*/*z*): 317 (14.3), 289 (7.9), 257 (9.1), 225 (8.4), 213 (8.5), 203 (42.8), 197 (30.5), 175 (37.4), 165 (63.9), 143 (27.5), 117 (100.0), 83 (15.7), 55 (12.7). Anal. Calcd for $C_{19}H_{34}O_6Si$: C, 59.04; H, 8.87. Found: C, 59.36; H, 9.11.

Catalyzed Diels−Alder Reactions. A solution of the catalyst (0.1 mmol) was added to ethyl glyoxylate (1.1 mmol, 112 mg) in toluene (2 mL). The mixture was stirred at a particular temperature (see Table 1) for 10 min. Then diene **6** (1.0 mmol, 284 mg) was added, and the resulting solution was stirred until TLC showed the completion of the reaction. Water (2 drops) was added to destroy the Lewis acid, and the mixture was then diluted with dichloromethane. The solution was filtered with suction through Celite, and the filter cake was washed several times with dichloromethane. The filtrate

was dried over $MgSO_4$ and concentrated under reduced pressure before being subjected to column chromatography.

Ethyl 2,5-Dideoxy-4,4-dimethyl-6,7-*O*-diacetyl-D-*ribo*-octonate (9a). Compound **8a** (300 mg, 1.06 mmol) and Amberlyst 15 ion-exchange resin (100 mg) in 10 mL of methanol was stirred and heated at 60 °C for 3 h. (Longer reaction time led to ester exchange; the ethyl ester was converted to the methyl ester). After being cooled and filtered, the reaction mixture was then diluted with dichloromethane and washed with water (2 × 2 mL). After evaporation of the solvent, acetylation of the residue with a mixture of acetic anhydride and pyridine (1:1.1, 2 mL) produced compound **9a** (345 mg, 0.95 mmol) in 90% yield. Compound **8c** was subjected to the same conditions as above, giving **9c** in 91% yield. Compound **9a**: $R_f = 0.30$ (petroleum ether−EtOAc 2:1). $[\alpha]^{20}_D$ +25.3 (*c*, 0.23, $CHCl_3$). IR (neat): 2966, 1743, 1317, 1244, 1197, 1050, 669 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.09 (1 H, dt, J = 6.4, 3.0 Hz, H-7), 4.48 (1 H, dd, J = 12.1, 3.0 Hz, H-8), 4.22 (1 H, dd, J = 12.1, 3.0 Hz, H-8), 4.21 (2 H, q, J = 7.2 Hz), 4.12 (1 H, dd, J = 12.2, 2.4 Hz, H-2), 3.70 (1 H, ddd, J = 11.9, 6.4, 2.4 Hz, H-6), 3.22 (3 H, s), 3.21 (3 H, s), 2.28 (1 H, m), 2.13 (1 H, m), 2.08 (3 H, s), 2.05 (3 H, s), 1.50 (2 H, m), 1.28 (3 H, t, J = 7.2 Hz). EIMS (*m*/*z*): 317 (M^+ − OEt, 1.0), 285 (3.2), 201 (26.9), 183 (8.9), 171 (58.2), 141 (11.8), 123 (49.2), 101 (15.4), 71 (15.8), 43 (100.0). HR EIMS calcd for $C_{14}H_{21}O_8$ (M^+ − OEt) 317.1236. Found: 317.1236.

Compound **9c**: R_f = 0.31 (petroleum ether−EtOAc, 2:1). $[\alpha]^{20}_D$ −22.4 (*c*, 0.34, $CHCl_3$). IR (neat): 2840, 1745, 1373, 1250, 1166, 1080, 99 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.16 (1 H, m, H-7), 4.38 (1 H, dd, J = 12.0, 3.8 Hz, H-8), 4.21 (1 H, dd, J = 12.0, 7.4 Hz, H-8), 4.10 (2 H, q, J = 7.1 Hz), 4.09 (1 H, dd, J = 12.2, 2.4 Hz, H-2), 3.78 (1 H, ddd, J = 12.0, 3.8, 2.1 Hz, H-6), 3.20 (3 H, s), 3.17 (3 H, s), 2.28 (1 H, dd, J = 13.5, 2.4 Hz, H-3), 2.10 (3 H, s), 2.02 (3 H, s), 1.89 (1 H, dd, J = 13.5, 2.1 Hz, H-5), 1.55 (1 H, dd, J = 13.3, 12.2 Hz, H-3), 1.41 (1 H, dd, J = 13.5, 12.0 Hz, H-5), 1.24 (3 H, t, J = 7.1 Hz). EIMS (*m*/*z*): 317(M^+ − OEt, 6.0), 257 (4.0), 243 (22.6), 199 (2.6), 183 (34.2), 165 (49.3), 157 (40.5), 123 (25.9), 113 (13.5), 97 (14.8). HR EIMS calcd for $C_{14}H_{21}O_8$ (M^+ − OEt) 317.1236. Found: 317.1200.

Ethyl 2,5-Dideoxy-4-*O*-(*tert*-butyldimethylsilyl)-5-hydroxy-6,7-*O*-isopropylidene-D-*glycero*-octonate (12). To 0.518 mL of 2.0 N borane in tetrahydrofuran at 0 °C under nitrogen was added 200 mg (0.518 mmol) of **8a** in 7 mL of anhydrous tetrahydrofuran. The reaction mixture was stirred at 0 °C for 30 min, before 2 mL of water, 1.5 mL of 20% sodium hydroxide solution, and finally 1.2 mL of 30% hydrogen peroxide were introduced in turn. The reaction mixture was then extracted with several portions of ether. The combined ethereal phases were washed with water and dried over anhydrous sodium sulfate. Flash chromatography (petroleum ether/EtOAc, 1:1, v/v) gave compound **12** as an oil (188 mg, 90%, yield): R_f = 0.30. IR (neat): 3600−3850, 2950, 2880, 1744, 1371, 1244, 1223, 1145, 1049, 700 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ 4.14 (2 H, q, J = 7.1 Hz), 4.10−3.80 (6 H, m), 3.54 (1 H, dd, J = 11.5, 6.0 Hz), 1.33 (3 H, s), 1.24 (3 H, s), 1.22 (3 H, t, J = 7.14 Hz), 0.86 (9 H, s), 0.08 (3 H, s), 0.07 (3 H, s). EIMS (*m*/*z*): 357 (M^+ − OEt, 19.2), 283 (19.8), 243 (29.7), 225 (47.6), 181 (58.3), 151 (64.4), 135 (44.4), 119 (37.2), 109 (33.1), 101 (37.9), 81 (83.9), 73 (100.0), 55 (57.6), 43 (87.6). HR EIMS calcd for $C_{18}H_{33}O_7Si$ 389.1996. Found 389.2025.

Ethyl 2,5-Dideoxy-4-*O*-(*tert*-butyldimethylsilyl)-6,7-*O*-isopropylidene-5-one-D-*glycero*-octonate (14). Compound **12** (100 mg, 0.25 mmol), pyridinium chlorochromate (320 mg), and activated molecular sieves (200 mg) in dry benzene (8 mL) were heated under refluxed for 1 h. The reaction mixture was filtered through a short silica gel column (benzene) to give compound **14** as an oil (79 mg, 80%): R_f = 0.33. $[\alpha]^{20}_D$: +18.9 (*c*, 1.78, $CHCl_3$). IR (neat): 2082, 2056.5, 1761, 1740, 1474, 1464, 1361, 1371, 1257, 1222, 1176, 1140, 1065, 1032, 655, 616 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ 4.53 (1 H, q, J = 6.3 Hz, H-7), 4.22 (1 H, dd, J = 12.2, 2.2 Hz, H-2), 4.15 (2 H, q, J = 7.1 Hz, OCH_2CH_3), 4.07 (1 H, dd, J = 8.7, 6.4 Hz, H-8), 4.00 (1 H, dd, J = 8.7, 5.9 Hz, H-8), 3.92 (1 H, dd, J = 11.3, 5.3 Hz, H-4), 3.39 (1 H, d, J = 6.6 Hz, H-6), 2.01 (1 H, m, H-3), 1.72 (1 H, q, J = 12 Hz, H-3), 1.39 (3 H, s), 1.32 (3 H, s), 1.22 (3 H, t, J = 7.1 Hz), 0.90 (9 H, s), 0.15 (3 H, s), 0.14 (3 H, s). EIMS (*m*/*z*): 387 (M^+ − 15, 1.0), 343 (8.8), 311 (7.1), 285 (100.0), 243 (36.8), 211 (11.0), 197 (17.9), 185 (4.4), 171 (13.2), 149 (23.6), 129 (12.4), 101 (85.9), 73 (55.8). HR EIMS calcd for $C_{18}H_{31}O_7Si$ (M^+ − CH_3) 387.1839. Found 387.1849.

Ethyl 2,5-Dideoxy-4-*O*-(*tert*-butyldimethylsilyl)-5-hydroxy-6,7-*O*-isopropylidene-D-*glycero*-octonate (13). To a mixture of sodium borohydride (76 mg, 2 mmol) and $CeCl_3 \cdot 7H_2O$ (75 mg, 0.2 mmol) in ethanol (15 mL) stirred at −15 °C was added dropwise ketone **14** (402 mg, 1 mmol, dissolved in 10 mL of EtOH). The addition funnel was rinsed with ethanol (3 mL), and the mixture was stirred at −15 °C for 3 h before 10 mL of water was added to quench the reaction. The mixture was extracted with several portions of ether. The combined ether layers were washed with water and dried over anhydrous sodium sulfate. Flash chromatography (petroleum ether/EtOAc, 1:1, v/v) gave compound **13** as an oil (280 mg, 70% yield): R_f = 0.33. $[\alpha]^{20}_D$: −12.2 (*c*, 0.26, $CHCl_3$). IR (neat): 3300, 2978, 1750, 1384, 1371, 1226, 1210, 1196, 1150, 1106, 1063, 881, 846, 514 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ 4.29 (1 H, q, J = 6.7 Hz, H-7), 4.14 (2 H, q, J = 7.1 Hz, OCH_2CH_3), 4.13−4.02 (2 H, m), 4.01 (1 H, dd, J = 8.5, 6.2 Hz, H-8), 3.93 (1 H, dd, J = 8.5, 5.5 Hz, H-8), 3.80 (1 H, dd, J = 0.5, 3.0 Hz), 3.40 (1 H, dd, J = 7.5, 1.2 Hz), 1.90 (2 H, m), 1.32 (3 H, s), 1.27 (3 H, s), 1.22 (3 H, t, J = 7.1 Hz, OCH_2CH_3), 0.90 (9 H, s), 0.12 (3 H, s), 0.11 (3 H, s). EIMS (*m*/*z*): 404(M^+, 0.5), 389 (M^+ − 15, 3.1), 345 (2.1), 309 (3.2), 257 (7.2), 243 (6.6), 197 (8.4), 169 (9.9), 101 (100.0). HR EIMS calcd for $C_{19}H_{36}O_7Si$: 404.2230. Found: 404.2184.

Ethyl and Methyl 2,6-Anhydro-3-deoxy-4,5:7,8-di-*O*-isopropylidene-D-*glycero*-D-*galacero*-D-*galacto*-octonate (17 and 18).[17] Compound **13** (404 mg, 1.0 mmol) and Amberlyst 15 ion-exchange resin (200 mg) in 100 mL of methanol was heated at 60 °C for 3 h. The mixture was then cooled, diluted with CH_2Cl_2, and washed with water (2 × 2 mL). After evaporation of the solvent, the residue was dissolved in a mixture of freshly distilled 2,2-dimethoxypropane (0.5 mL), and anhydrous acetone (3 mL), *p*-toluenesulfonic acid (1 mg), and $MgSO_4$ (1.0 g) were added. After stirring at room temperature for 3 h, the mixture was concentrated, and the residue was chromatographed on silica gel with ethyl acetate/petroleum (1:3) as eluant, affording **17** (15.8 mg) and **18** (271.8 mg) as an oil in 95% yield. Compound **17**: R_f = 0.33. $[\alpha]^{20}_D$ +29.8 (*c*, 1.5, $CHCl_3$). IR (neat): 2978, 1750, 1384, 1371, 1226, 1063 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ 4.43 (1 H, dt, J = 8.3, 5.9 Hz, H-7), 4.27 (1 H, dt, J = 7.4, 5.7 Hz, H-4), 4.19 (1 H, dd, J = 5.7, 2.1 Hz, H-5), 4.17 (2 H, m, OCH_2CH_3), 4.13 (1 H, m, H-2), 4.03 (2 H, m, H-8), 3.71 (1 H, dd, J = 7.4, 2.1 Hz, H-6), 2.14 (1 H, ddd, J = 13.6, 6.0, 3.7 Hz, H-3), 1.80 (1 H, ddd, J = 13.6, 9.7, 8.4 Hz, H-3), 1.42 (3 H, s), 1.35 (3 H, s), 1.29 (3 H, s), 1.28 (3 H, s), 1.23 (3 H, t, J = 7.1 Hz). EIMS (*m*/*z*): 363 (M^+ + 1, 0.5), 347 (M^+ − 15, 15.0), 305 (6.1), 269 (2.8), 247 (9.6), 229 (13.5), 211 (12.4), 203 (26.6), 75 (100.0). Compound **18**: R_f = 0.30. $[\alpha]^{20}_D$ +28.8 (*c*, 1.5, $CHCl_3$). (lit.[18] +30.4 (*c*, 1.5, $CHCl_3$)). IR (neat): 2940, 1765, 1369, 1240, 1213, 1050 cm^{-1}. ^1H NMR (300 MHz, CD_3COCD_3): δ 4.43 (1 H, dt, J = 8.1, 5.8 Hz, H-7), 4.26 (1 H, ddd, J = 7.5, 6.0, 5.4 Hz, H-4), 4.20 (1 H, dd, J = 5.8, 2.1 Hz, H-5), 4.17 (1 H, dd, J = 9.5, 3.8 Hz, H-2), 4.05 (1 H, dd, J = 8.6, 6.0 Hz, H-8), 4.03 (1 H, dd, J = 8.6, 5.3 Hz, H-8), 3.70 (1 H, dd, J = 5.8, 2.1, H-6), 3.69 (3 H, s, OCH_3), 2.19 (1 H, ddd, J = 13.6, 5.8, 3.8 Hz, H-3), 1.81 (1 H, ddd, J = 13.6, 9.5, 8.2 Hz, H-3), 1.41 (3 H, s), 1.37 (3 H, s), 1.29 (3 H, s), 1.27 (s, 3 H). ^{13}C NMR (75 MHz, CD_3COCD_3): δ 171.74, 109.60, 109.55, 76.57, 75.25, 73,13, 72.36, 72.06, 67.37, 52.10, 31.73, 27.92, 27.05, 26.30, 25.74. MS (*m*/*z*): 301 (M − 1, 64.5), 243 (20.7), 199 (4.6), 183 (100.0), 155 (12.5), 149 (13.2), 123 (27.8), 113 (16.9), 101 (76.8).

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Supporting Information Available: Reproductions of ^{1}H NMR for compounds **8a**, **8b**, **8c**, **9a**, **9c**, **12**, **13**, **15**, **16**, **17**, **18**; 2D NMR for compounds **8a**, **8b**, **8c**, **9c**; ^{13}C NMR for compound **17**, **18** (16 pages). This material is contained in libraries on microfiche, immediately follows this article in microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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