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# THE ASYMMETRIC EPOXIDATION OF DIVINYL CARBINOLS: THEORY AND APPLICATIONS†

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**Abstract** The asymmetric epoxidation of symmetric divinyl carbinols is illustrative of a reaction process that combines an initial asymmetric synthesis with a subsequent kinetic resolution to provide products with extraordinary levels of enantiomeric purity. The application of this process to the asymmetric synthesis of natural products is presented herein.

Recently, we described a mathematical model for a general reaction process that involves the combination of a group and face selective addition reaction.[2] These processes couple an initial asymmetric synthesis with a subsequent kinetic resolution to afford products with extraordinary levels of enantiomeric purity. In this paper, we discuss the group and face selective addition reaction and report on applications of the process to syntheses of the natural products, riboflavin (vitamin $B_2$) and (+)-KDO.

The reaction class under investigation involves the reaction of a chiral, nonracemic reagent **R** with an achiral or meso substrate **S** (Figure 1). The substrate **S** contains a prostereogenic atom equipped with paired ligands that are enantiotopic and unsaturated. Vinyl groups are indicated, but other unsaturated pi systems (alkenes, carbonyls, etc.) can be substituted. The reagent, or part of the reagent, can undergo addition to any one of the four heterotopic faces in the substrate to give four initial products $\mathbf{X_i}$. Since one unsaturated group remains in each product $\mathbf{X_i}$, a second addition of the reagent **R** can occur to give four possible secondary products $\mathbf{Z_i}$.

Note that the products $\mathbf{X_1}$ and $\mathbf{X_3}$ (and $\mathbf{X_2}$ and $\mathbf{X_4}$) are enantiomers. The ratio of $\mathbf{X_1/X_3}$, and thus the enantiomeric excess (ee), will be associated with the degree of group selectivity in this reaction. The value of $\mathbf{X_1/X_3}$ is expected to vary with time, since each compound can be converted to a double addition product $\mathbf{Z_i}$, and the rate of formation ($\mathbf{S + R \rightarrow X_i}$) and "destruction" ($\mathbf{X_i + R \rightarrow Z_1}$) of each product $\mathbf{X_i}$ will differ. For example, if $k_1 > k_j$ (j = 2,3,4), the major enantiomer $\mathbf{X_1}$ will have the "slow reacting" unsaturated group exposed, whereas the minor enantiomer $\mathbf{X_3}$ will have the "fast reacting" unsaturated group available for a second addition reaction. The minor enantiomer $\mathbf{X_3}$ is thus expected to be selectively "destroyed", and the ratio $\mathbf{X_1/X_3}$ is expected to increase as the reaction proceeds. *In other words, the first reaction converts an achiral substrate with a prostereogenic atom into a chiral, nonracemic product (asymmetric synthesis) and the second reaction enhances the ee via a kinetic resolution .*

The Sharpless asymmetric epoxidation (AE) reaction[3] was examined with several suitable substrates and shown to provide epoxy alcohol products whose enantiomeric purity increased as the reaction proceeded towards completion; a result that is in accord with a mathematical model[2] of the reaction process. For example, in the epoxidation of 2,4-dimethyl-1,4-pentadien-3-ol, separation of the derived Mosher esters

† **Dedicated to Professor David Ollis on the occasion of his 65th birthday.**

via capillary GC allowed for a highly accurate assessment of the ee, and, as can be seen in the data presented in Table 1, the amount of the minor isomer present became immeasurably small.

Figure 1 General Outline of Face and Group Selective Addition Reaction

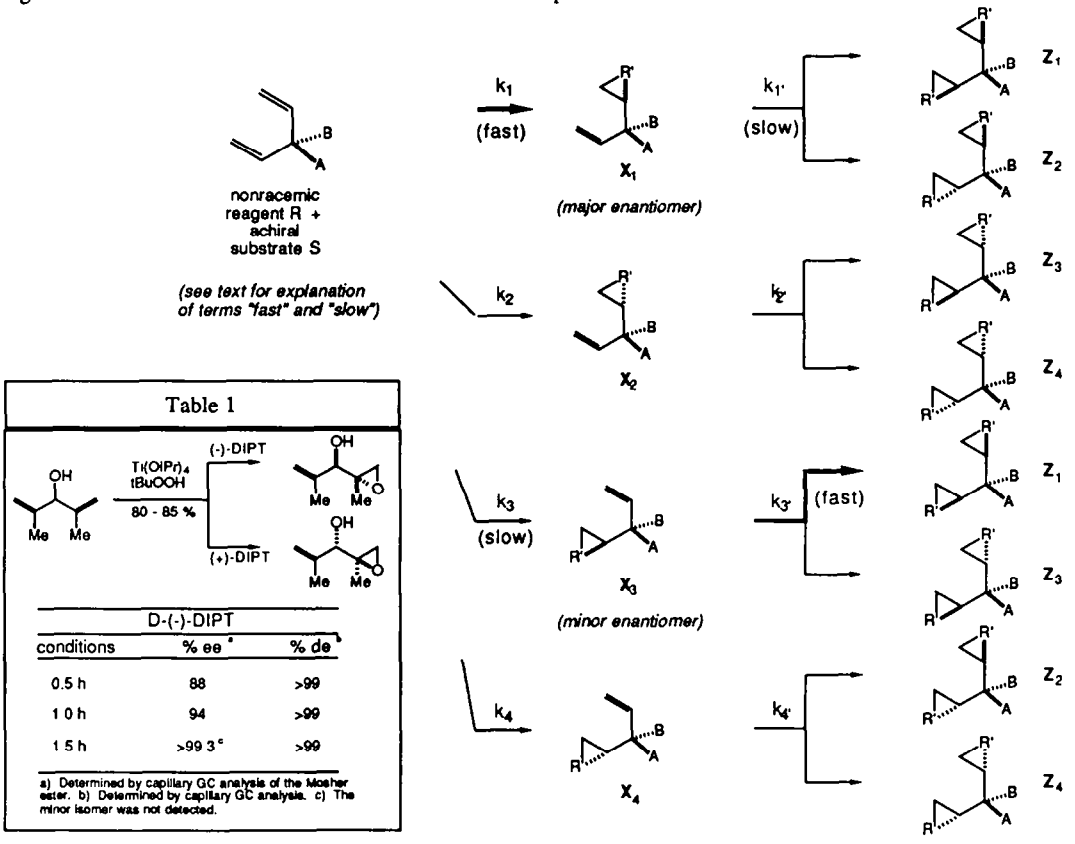



Table 1




| D-(-)-DIPT | | |
|---|---|---|
| conditions | % ee [a] | % de [b] |
| 0.5 h | 88 | >99 |
| 1.0 h | 94 | >99 |
| 1.5 h | >99 3 [c] | >99 |

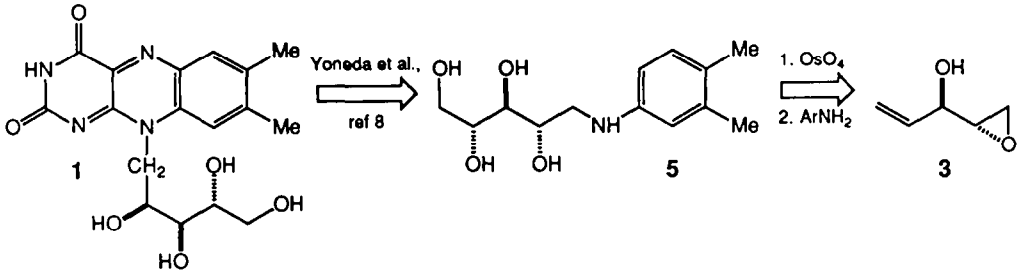
a) Determined by capillary GC analysis of the Mosher ester. b) Determined by capillary GC analysis. c) The minor isomer was not detected.

As an illustration of the utility of this reaction process, both enantiomers of riboflavin **1** were prepared from the inexpensive and simple starting material divinylcarbinol (Scheme 1).[4,5] This compound was examined in the earlier investigation and shown to provide enantiomeric monoepoxides **2** (= ent-**3**) or **3** with high enantiomeric purity.[2] Using the catalytic Sharpless AE procedure, **2** or **3** can be obtained in 80-85% yield on a 14g scale and 55-60% yield on a 25 g scale.

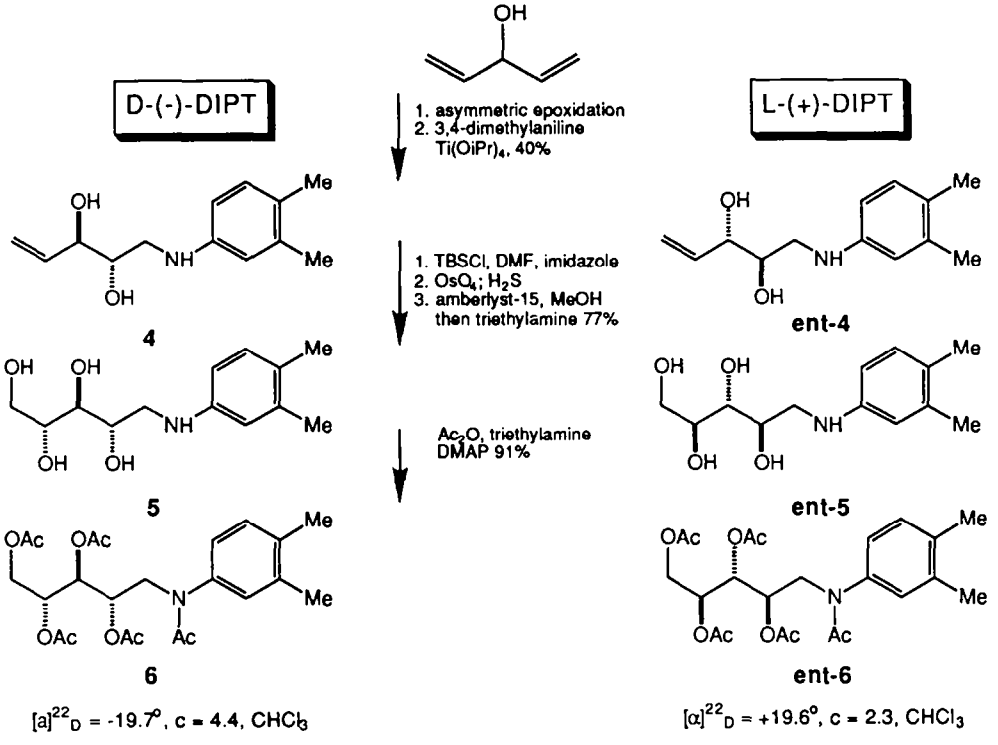
All attempts to isolate the epoxy triol derived from **3** via osmylation were unsuccessful, possibly owing to the polarity and water solubility of the product. The opening of epoxy alcohol **3** at the terminal position, however, was readily accomplished *via* the Sharpless procedure.[6] Thus, treatment of **3** with 3,4-dimethylaniline in the presence of titanium (IV) tetraisopropoxide furnished the amino diol **4**, albeit in

modest yield. The regiochemical outcome of this reaction is consistent with related reactions involving terminal epoxides.[4,6]

Scheme 1




Scheme 2



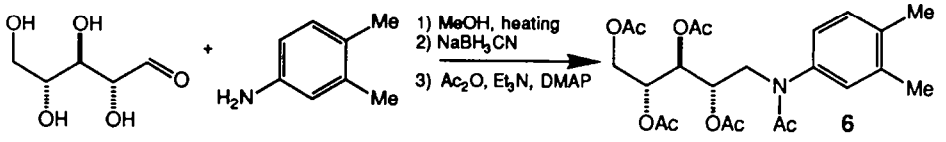

$[a]^{22}_D$ = -19.7°, c = 4.4, $CHCl_3$

$[\alpha]^{22}_D$ = +19.6°, c = 2.3, $CHCl_3$

The direct introduction of the final stereocenter of riboflavin was next attempted *via* an osmylation reaction. As was the case with epoxy alcohol **3**, no useful amounts of products could be produced. After some experimentation, it was found that the bis(t-butyldimethylsilyl) ether of **4** could be osmylated quantitatively under stoichiometric conditions to provide the desired diol, apparently as a single

diastereomer (Scheme 2).[7] Deprotection proceeded in quantitative yield using Amberlyst-15 in methanol to provide the amino tetraol **5**. The per-acetate **6** (and ent-**6**) was found to be identical ($^1H$ and $^{13}C$ NMR, IR, and MS) with the material produced from naturally occurring ribose, as shown in Scheme 3.

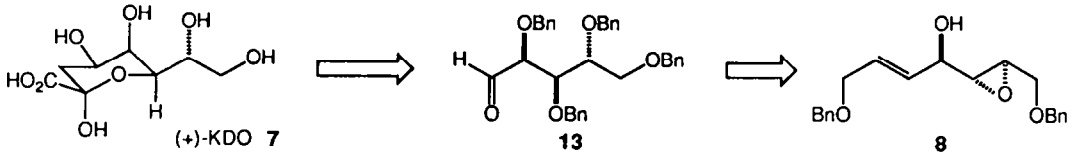
Scheme 3



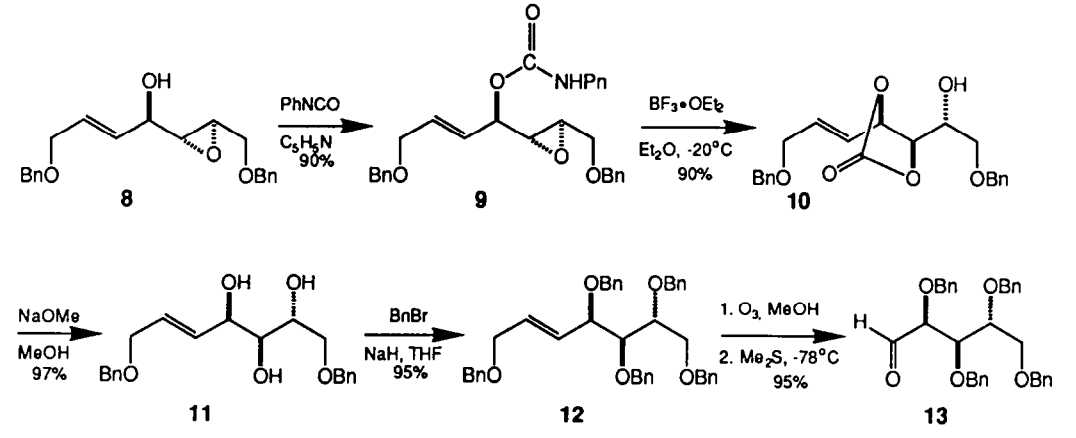

Thus, in five steps from divinylcarbinol, the amino tetraol **5** (and ent-**5**) has been prepared in 31% overall yield. Since **5** has been converted into riboflavin by several groups,[8] the work presented above constitutes a formal total synthesis of both (+) and (-)- riboflavin.

As a second illustration of group and face selective reactions, we next detail the asymmetric synthesis of 3-deoxy-D-manno-2-octulosonic acid **7** ((+)-KDO) Scheme 4).[9-11] (+)-KDO is the ketosidic component of gram-negative bacteria lipopolysaccharides.

Scheme 4



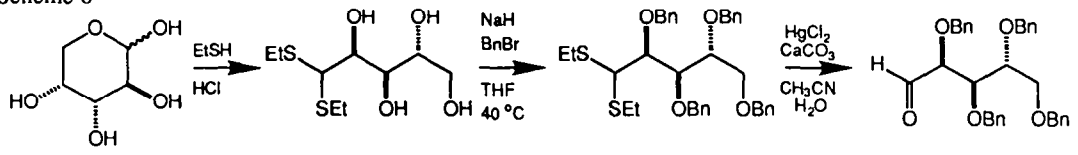

Scheme 5




The extraordinary high enantiomeric purity of monoepoxide **8**, derived from the corresponding dialkenyl carbinol via Sharpless AE, was described in our earlier study.[2] Reaction of **8** with phenyl isocyanate in

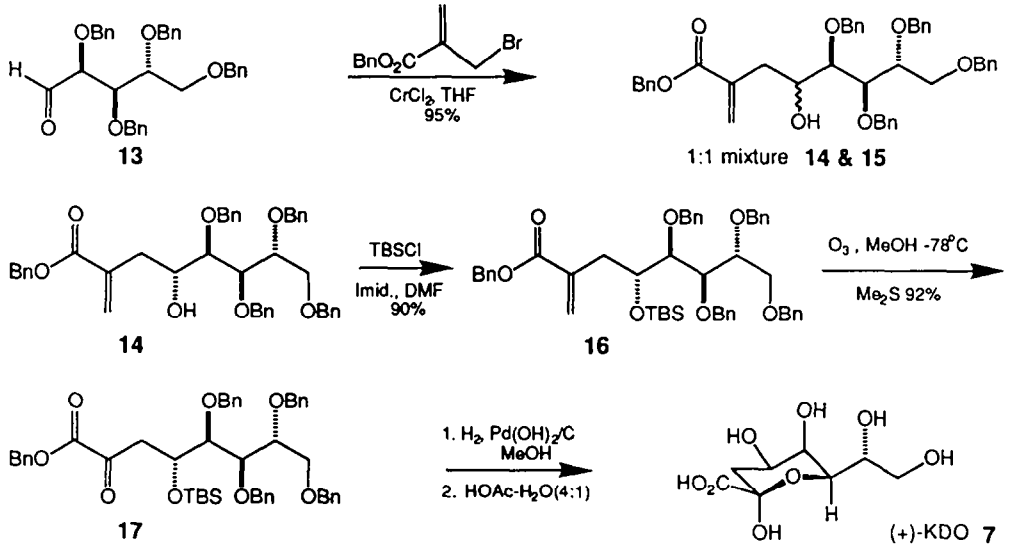
pyridine afforded the phenylurethane derivative **9** (Scheme 5). Epoxide opening was achieved by treatment of **9** with $BF_3 \bullet OEt_2$ in ether at -20°C, followed by hydrolysis of the intermediate iminocarbonate, to afford the carbonate **10** in 90% yield. After deacylation with NaOMe in MeOH, the resulting triol **11** was converted into pentabenzylether **12** in 95% yield. Ozonolysis of **12**, followed by reduction with $Me_2S$, afforded the fully protected D-arabinose derivative **13** in 95% yield, which is identical with the same aldehyde obtained from D-arabinose in all aspects (Scheme 6).

Scheme 6



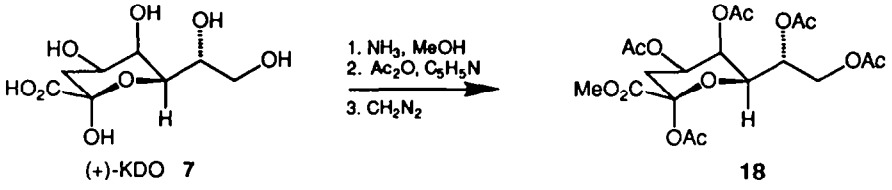

With aldehyde **13** in hand, the construction of the α-ketoester **17** was investigated by an aldol reaction with several pyruvate enolate equivalents (Scheme 7). After many unsuccessful attempts, our attention was focused on the coupling of a methacrylate anion with aldehyde **13**. The best procedure utilized the Cr(II) mediated coupling of benzyl α-(bromomethyl)-acrylate to **13**.[12] Compounds **14** and **15** were isolated in 95% yield as a near 1:1 mixture which were separated by HPLC or flash chromatography. The stereochemistry of the products was determined by the conversion of **14** into D-(+)-KDO.

Scheme 7



The less mobile diastereomer **14** was silylated with TBSCl and imidazole in DMF to provide silyl ether **16**. Ozonolysis of **16**, followed by reduction with $Me_2S$, afforded α-keto ester **17** in 82% overall yield from **14**. Deprotection was accomplished by hydrogenolysis, followed by treatment with mild acid, to give synthetic (+)-KDO **7**, which was fully characterized as its peracetylated methyl ester. Peracylation of the synthetic KDO ammonium salt, followed by esterification, provided **18**, whose NMR spectrum matches that of an authentic sample (Scheme 8).[13]

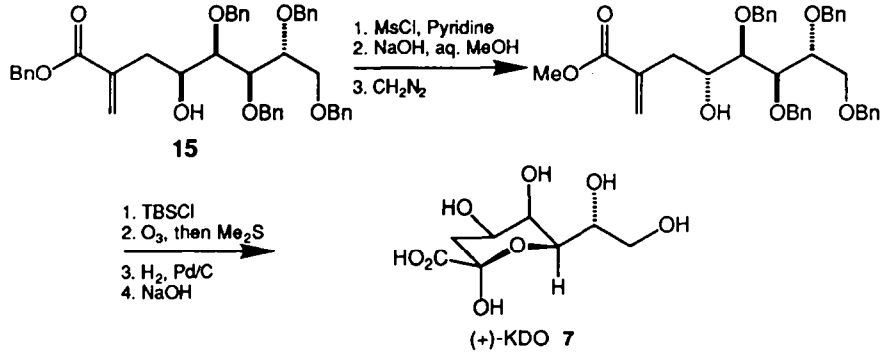
Scheme 8




(+)-KDO **7** **18**

The diastereomeric addition product **15** was also converted into (+)-KDO by a reaction sequence shown in Scheme 9 and parallels our earlier studies that resulted in the total synthesis of invictolide.[14] In this manner, both addition products **14** and **15** were converted into (+)-KDO.

Scheme 9




**15**

(+)-KDO **7**

In conclusion, we have demonstrated the utility of group and face selective addition reactions to the syntheses of enantiomerically pure natural products. Further progress in this area is ongoing and will be reported in due course.

## Experimental Section

Proton magnetic resonance spectra ($^1H$ NMR) were recorded on a Bruker WM-250 (250 MHz) instrument. All spectra were taken in $CDCl_3$ and chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane using residual chloroform (δ = 7.27 ppm) as an internal standard. Spectra are described as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m =

multiplet, br = broad), coupling constants (Hz), and integration. Carbon magnetic resonance spectra ($^{13}C$ NMR) were recorded on a Bruker WM-250 (62.9 MHz) instrument using broad band decoupling of protons. Chemical shifts are reported in parts per million downfield from tetramethylsilane using residual chloroform ($\delta$ = 77.0 ppm) as an internal standard.

Infrared spectra (IR) were recorded on a Nicolet 5SX or 5PC FT-IR spectrometer. *V*max are reported in reciprocal centimeters ($cm^{-1}$). Bands are characterized as s = strong, m = medium, w = weak, sh = shoulder, or br = broad. Mass spectra (MS) were recorded on a Hewlett-Packard 5985-GC/MS system equipped with a 2% OV-101 column (3 ft x 1/4 in. x 2 mm) on Chromosorb WHP 100/120. Samples were ionized by electron impact (EI) at 20 eV. The molecular ion and significant fragments are reported as relative intensities in the form m/e. High resolution mass spectra (HRMS) were recorded on a Kratos MS-80RFA instrument. Elemental combustion analysis were performed by Atlantic Microlab, Inc., Norcross, Georgia.

**(2R, 3S)-1,2-Epoxypent-4-en-3-ol (2).** To a flame dried 1 L round bottom flask fitted with a large magnetic stirbar were added 4Å molecular sieves (MS) (4.3 g, 2-3 micron, powdered) and 250 mL of methlyene chloride. The flask was placed under nitrogen and cooled to -23 °C (dry ice/carbon tetrachloride). Titanium tetraisopropoxide (5.0 mL, 17 mmol) and L-(+)-diisopropyltartrate (4.5 mL, 21 mmol) were added *via* syringe, in that order. After stirring 10 min at -23 °C , divinylcarbinol (20.0 g, 238 mmol) was added *via* cannula, followed by t-butylhydroperoxide (160 mL, 3.0 M in isooctane, 480 mmol) in several portions *via* syringe. The flask was then placed in a -15 °C freezer and stirred for 118 hr. Sodium sulfate (17 mL, saturated aqueous) was added at -15 °C and the mixture was diluted with 250 mL of ether. The flask was then removed from the freezer and stirred vigorously at room temperature for 2 hr under nitrogen. The resulting slurry was filtered through a pad of Celite with exhaustive ethereal washing. The pad was then scraped into an Erlenmeyer flask, heated gently with ether, and filtered through a new Celite pad. Most of the solvent was removed from the combined filtrates *via* rotary evaporation with cooling to avoid loss of the slightly volatile product. The resulting oil was subjected to flash chromatography using pentane/ether (2/1), followed by careful solvent removal of the product containing fractions under reduced pressure. Distillation of the resultant liquid under aspirator pressure afforded 23.6 g of product that was ca. 50% pure. This oil was again subjected to flash chromatography (1/1 pentane/ether, then ether) in two portions to finally yield, after careful solvent removal, 13.1 g (55%) of pure mono epoxy alcohol. $[\alpha]^{23}_D$ = + 48.8°, c = 0.73, $CHCl_3$. The enantiomer 3 was prepared in a similar manner using D-(-)-diisopropyltartrate, $[\alpha]^{21}_D$ = -46.4°, c = 1.15, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): $\delta$ 5.89-5.75 (ddd, J = 17.2, 10.5, 6.2, 1H); 5.34 (dt, J = 17.2, 1.4, 1H); 5.22 (dt, J = 10.5, 1.3, 1H); 4.26 (bs, 1H); 3.05 (dd, J = 3.1, 3.3, 1H); 2.78-2.70 (m, 2H); 2.61 (bs, 1H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): $\delta$ 135.6, 117.3, 70.3, 53.9, 43.5.

IR (film): 3400 (broad, s), 3019 (s), 1108 (s).

MS (EI, 20 eV): 99.1 ($(M-1)^+$, 0.4), 57.1 (100).

**(2S, 3R)-N-(3',4'-dimethylphenyl)-1-aminopent-4-en-2,3-diol (4).** To a solution of divinylcarbinol epoxide 3 (0.10 g, 1.0 mmol) in 5 mL of tetrahydrofuran under nitrogen was added 3,4-dimethylaniline (0.15 g, 1.2

mmol), followed by titanium(IV)isopropoxide (0.90 mL, 3.0 mmol). The mixture was stirred at room temperature for 90 min, then diluted with 20 mL of ether and sodium hydroxide (3 mL, 10% in brine). After 5 hr of vigorous stirring the mixture was passed through a Celite plug with extensive ethereal washing. The combined filtrates were dried over $MgSO_4$, filtered, and concentrated. The product (0.1072 g, clear yellow oil, 48%) was isolated *via* flash chromatography (75% ether in petroleum ether). $[\alpha]^{22}_D$ = -1.59°, c = 1.83, $CHCl_3$. The enantiomer was prepared in a similar manner, $[\alpha]^{23}_D$ = +1.22°, c = 1.64, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 6.97 (d, J = 8.0, 1H), 6.51 (broad s, 1H), 6.45 (dd, J = 8.0, 2.5, 1H), 5.94 (ddd, J = 17.2, 10.4, 6.4, 1H), 5.38 (dt, J = 17.2, 1.4, 1H), 5.28 (dt, J = 10.4, 1.3, 1H), 4.27 (m, 1H), 3.87 (m, 1H), 3.75 (broad s, 3H), 3.26 (dd, J = 12.9, 7.9, 1H), 2.23 (s, 3H), 2.20 (s, 3H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 146.1, 137.2, 136.4, 130.3, 126.3, 117.1, 115.7, 111.3, 74.9, 72.2, 46.1, 19.8, 18.5.

IR (film): 3380 (broad, s), 2974 (m), 2921 (s), 2863 (m), 1618 (s), 1508 (s), 1448 (m), 1384 (w), 1320 (m), 1261 (w), 1217 (w), 1120 (m), 1078 (m), 994 (m), 926 (m), 804 (m).

MS (DIP, 20 eV): 221.2 ($M^+$, 22.4), 164.2 (4.8), 146.1 (2.2), 135.2 (10.1), 134.2 (100), 121.2 (6.3).

**(2S, 3R)-N-(3',4'-Dimethylphenyl)-1-amino-2,3-bis (t-Butyldimethylsilyloxy)-pent-4-ene.** To a solution of diol 4 (0.280 g, 1.27 mmol) in 15 mL of DMF was added tert-butyldimethylsilyl chloride (0.645 g, 4.28 mmol), followed by imidazole (0.305 g, 4.48 mmol). The reaction mixture was stirred under nitrogen for 28 hr at room temperature, then diluted with hexanes, and washed once with aqueous sodium bicarbonate. The aqueous phase was back extracted once with hexanes. The combined organics were dried over $Na_2SO_4$, filtered, and concentrated. Flash chromatography (3% ethyl acetate in hexanes) provided 0.4612 g (81%) of N-(3',4'-dimethylphenyl)-1-amino-2(R),3(R)-t-butyldimethylsilyloxypent-4-ene as a clear colorless oil. $[\alpha]^{23}_D$ = +9.57°, c = 2.32, $CHCl_3$. The enantiomer was prepared in a similar manner, $[\alpha]^{22}_D$ = -8.77°, c = 4.45, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 6.95 (d, J = 8.0, 1H), 6.45 (d, J = 2.4, 1H), 6.39 (dd, J = 8.0, 2.4, 1H), 5.90 (ddd, J = 17.2, 10.4, 6.5, 1H), 5.26 (dt, J = 17.2, 1.5, 1H), 5.18 (dt, J = 10.4, 1.0, 1H), 4.17 (m, 1H), 3.85 (broad s, 1H), 3.77 (m, 1H), 3.29 (dd, J = 12.2, 4.6, 1H), 3.18 (dd, J = 12.2, 4.2, 1H), 2.22 (s, 3H), 2.18 (s, 3H), 0.93 (s, 9H), 0.92 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 147.3, 139.9, 137.6, 130.7, 125.6, 116.6, 115.4, 111.0, 78.0, 75.4, 46.8, 26.5, 20.5, 19.2, 18.7, -3.7, -3.8, -4.0, -4.3.

IR (film): 2955 (s), 2929 (s), 2894 (m), 2886 (m), 2857 (s), 1617 (m), 1511 (m), 1472 (m), 1255 (s), 1100 (s), 835 (s), 777 (s).

MS (EI, 20 eV): 452.1 (5.7), 451.1 (15.5), 450.1 ($M^+$, 28.1), 392.9 (9.2), 279.7 (10.0), 278.7 (23.9), 197.5 (22.1), 186.6 (9.9), 185.5 (6.2), 184.5 (30.4), 147.4 (8.2), 146.4 (22.4), 135.4 (35.6), 134.4 (100), 133.3 (15.9), 128.3 (7.7), 127.5 (39.4), 73.3 (20.9).

**(2S, 3S, 4R)-N-(3',4'-dimethylphenyl)-1-amino-2,3-bis(t-butyldimethylsilyloxy)-pentan-4,5-diol.** A solution of the bis(silylether) of **4** (0.146 g, 0.325 mmol) in 5 mL of THF/pyridine (4/1) was treated with osmium tetroxide (1.0 mL, 0.39 M in THF, 0.39 mmol) and stirred at room temperature under nitrogen overnight. The mixture was diluted with methanol and gaseous $H_2S$ was bubbled through the solution for 30 min. After flushing with nitrogen, the solvent was removed under reduced pressure, and the residue purified *via* flash chromatography (17% ethyl acetate in hexanes) to provide 0.1533 g (98%) of N-(3',4'-dimethylphenyl)-1-amino-2(R),3(R)-t-butyldimethylsilyloxy-4(R),5-dihydroxypentane as a clear colorless oil. $[\alpha]^{23}_D$ = +8.47°, c = 3.16, $CHCl_3$. The enantiomer was prepared in a similar manner, $[\alpha]^{21}_D$ = -8.52°, c = 4.02, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 6.96 (d, J = 8.0, 1H), 6.49 (d, J = 2.4, 1H), 6.42 (dd, J = 8.0, 2.4, 1H), 4.07 (m, 1H), 3.95-3.65 (m, 6H), 3.25 (m, 2H), 2.21 (s, 3H), 2.17 (s, 3H), 0.94 (s, 9H), 0.92 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H), 0.097 (s, 3H), 0.079 (s, 3H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 145.7, 137.3, 130.3, 126.4, 115.6, 111.3, 76.1, 74.4, 71.8, 63.8, 47.4, 26.0, 25.9, 20.0, 18.7, 18.1, -4.1, -4.4, -4.6, -4.8.

IR (film): 3397 (broad, m), 2954 (s), 2929 (s), 2885 (m), 2857 (s), 1619 (m), 1511 (m), 1472 (m), 1254 (s), 1080 (broad, s), 837 (s), 778 (s).

MS (DIP, 20 eV): 484.4 (24.6), 483.4 ($M^+$, 62.4), 426.4 (43.5), 187.2 (14.5), 135.2 (20.6), 134.2 (100), 133.2 (43.3).

**(2S, 3S, 4R)-N-(3',4'-dimethylphenyl)-1-aminopentan-2,3,4,5-tetraol (5).** To a solution of the bis(silyl ether) diol (83.9 mg, 0.173 mmol) in 10 mL of methanol was added Amberlyst-15 resin (0.250 g, active form). The biphasic mixture was stirred at ambient temperature for 2 days, then the methanol was removed *via* pipette, and discarded. The resin was washed with 5 mL of methanol, and the methanol discarded. The resin was then washed repeatedly with methanol/triethylamine, until tlc analysis showed no further product in the wash layers. The combined extracts were concentrated to give 42.5 mg (96%) of the white solid, (2S, 3S, 4R)-N-(3',4'-dimethylphenyl)-1-amino-2,3,4,5-tetrahydroxypentane, which could be recrystallized from methanol (m.p. 135-137°C) to provide an analytical sample.

Analysis: Calculated for $C_{13}H_{21}NO_4$; C 61.16, H 8.29, N 5.49; Found C 61.14, H 8.28, N 5.47.

**Peracetate (6).** To tetraol **5** (42.5 mg, 0.167 mmol) in 3 mL of methylene chloride, was added triethylamine (0.20 mL, 1.4 mmol) and acetic anhydride (0.110 mL, 1.16 mmol), followed by a trace of N,N-dimethylaminopyridine. The initial biphasic mixture was stirred overnight at ambient temperature under a nitrogen atmosphere. The homogeneous reaction was then quenched with several drops of methanol and

solvent removed under reduced pressure. Flash chromatography was performed with diethylether to provide 60.5 mg (78%) of the peracetylated product as a clear colorless oil. $[\alpha]^{22}_D$ = -19.7°, c = 4.38, $CHCl_3$. The enantiomer was prepared in a similar manner, $[\alpha]^{23}_D$ = +19.6°, c = 2.28, $CHCl_3$. The data gathered for either enantiomer was identical to the peracetate prepared from D-ribose (see text).

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.14 (d, J = 7.9, 1H), 6.90 (broad s, 1H), 6.87 (dd, J = 7.9, 1.9, 1H), 5.31 (d, J = 6.4, 2H), 5.20 (m, 1H), 4.29 (dd, J = 12.3, 3.1, 1H), 4.11 (dd, J = 12.3, 5.9, 1H), 4.06-3.84 (m, 2H), 2.26 (s, 6H), 2.05 (s, 3H), 2.03 (s, 6H), 1.91 (s, 3H), 1.80 (s, 3H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 171.0, 170.5, 170.1, 169.8, 169.6, 141.2, 138.2, 136.5, 130.8, 128.9, 125.2, 77.2, 70.8, 70.4, 69.5, 62.0, 48.5, 22.4, 20.6, 20.5, 20.4, 19.5, 19.1.

IR (film): 1746 (s), 1664 (m), 1504 (w), 1370 (m), 1216 (s), 1047 (m), 604 (w).

MS (EI, 20 eV): 465.3 ($M^+$, 30.5), 423.3 (22.4), 345.2 (31.1), 303.2 (19.1), 260.2 (31.4), 218.2 (41.0), 176.2 (27.6), 134.2 (100).

**(2S, 3S, 4R)-N-(3',4'-Dimethylphenyl)-1-aminopentan-2,3,4,5-tetraol (5).** To a solution of D-ribose (6.0 g, 40 mmol) in 50 mL of methanol in a 250 mL round bottom flask fitted with a magnetic stirbar, heating mantle, reflux condenser and nitrogen line was added 3,4-dimethylaniline (4.89 g, 40.3 mmol) . After 3 hr at reflux, the clear orange mixture was cooled to ambient temperature, causing the entire reaction mixture to solidify. A portion of this solid (about 10%) was transferred to a 250 mL round bottom flask and the solvent removed with warming. The resultant solid was dissolved in 10 ml of MeOH and gently warmed. Sodium cyanoborohydride (0.6 g, 9.55 mmol) was then added. After 2 hr of gentle heating under nitrogen, the solvent was removed. The oily residue was dissolved in hot water and acidified with 1 M HCl. The solution was extracted with ether and the ethereal layers discarded. Solid KOH was then added and the product was extracted with 3 portions of ethyl acetate. The combined extracts were dried over $MgSO_4$, filtered, and concentrated. The residual solid was recrystallized from methanol to give 0.350 g of a white solid, m.p. = 137-139°C. This solid was fully characterized at the per-acetate.

**Peracetate (6).** To a 25 mL pear shaped flask containing **5** (10.2 mg, 0.040 mmol, derived from D-ribose) in 2 mL of methylene chloride, was added acetic anhydride (0.020 mL, 0.212 mmol), triethylamine (0.033 mL, 0.237 mmol) and a catalytic amount of N,N-dimethylaminopyridine. The initially biphasic mixture was stirred at ambient temperature under nitrogen overnight. The reaction was then diluted with ether and passed through a plug of silica. Solvent was removed under reduced pressure and the residue purified by flash chromatography (diethylether) to give 18.6 mg (quantitative) of a colorless oil. $[\alpha]^{21}_D$ = -16.7°, c = 1.86, $CHCl_3$. Data gathered for this compound was identical to material prepared *via* total synthesis.

**Epoxy Alcohol (8).** To a cold (-23 °C) solution of titanium tetraisopropoxide (3.9 mL, 13 mmol) in 100 mL of methylene chloride was added D-(-)-diisopropyl tartrate (3.2 mL, 15 mmol). After 10 min, the alcohol (3.5 g, 11 mmol) was added, followed by t-butylhydroperoxide (4.0 mL, 5.2 M in toluene, 21 mmol). After 8 hr at -23 °C, the reaction was treated with 30 mL of a 10% aqueous tartaric acid solution. This mixture was

stirred for 30 min at -23 °C, then 90 min at ambient temperature. The organic layer was separated, washed with 20 mL of water, and dried over sodium sulfate. After concentration, the residue was diluted with 150 mL of ether and treated with 40 mL of 1 M sodium hydroxide for 30 min at 0 °C. The ether layer was then separated, washed with 20 mL of water, and dried over sodium sulfate. Concentration was followed by flash chromatography (1:1 hexane/EtOAc) to afford 3.46 g (94%) of the epoxy alcohol **8** as a yellow oil. $[\alpha]^{23}_D$ = -6.0°, c = 1.0, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.26-7.40 (m, 10H), 5.97 (dtd, J = 14.7, 5.3, 0.9 Hz, 1H), 5.76 (ddt, J = 14.7, 6.4, 1.3 Hz, 1H), 4.60 (d, A of AB, J = 12.0 Hz, 1H), 4.54 (d, B of AB, J = 12.0 Hz, 1H), 4.53 (s, 2H), 4.07 (dd, J = 5.4, 0.7 Hz, 2H), 3.80 (dd, J = 11.6, 2.7 Hz, 1H), 3.45-3.53 (m, 2H), 3.29 (m, 1H), 3.06 (dd, J = 3.0, 2.4 Hz, 1H).2.0 (br, 1H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 138.04, 137.74, 130.13, 129.63, 128.36, 127.69, 127.61, 73.21, 72.33, 69.77, 69.48, 69.15, 57.27, 53.61.

IR ($CHCl_3$): 3420 (br), 2856 (m), 1496 (w), 1453 (m), 1363 (w), 1101 (s), 1072 (m), 1027 (m), 973 (m), 738 (s), 698 (s).

**1,7-(Bisbenzloxy)-4-[(N-phenylcarbamoyl)-oxy]-5,6-epoxy-2-ene (9).** A solution of epoxy alcohol **8** (3.41 g, 10.0 mmol) in 100 mL of methylene chloride was treated with pyridine (4.0 mL, 50 mmol) followed by phenyl isocyanate (2.17 mL, 20.0 mmol) at room temperature. After stirring overnight, all volatiles were removed *in vacuo*. The residue was dissolved in 100 mL of chloroform and filtered through a pad of silica gel. Concentration was followed by flash chromatography (1:1 hexane/EtOAc) to give 4.13 g (90%) of homogeneous product. $[\alpha]^{23}_D$ = -10.6°, c = 4.2, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.28-7.40 (m, 15 H), 6.63 (s, 1H), 6.02 (dt. J = 15.7, 5.1 Hz, 1H), 5.79 (ddt, J = 15.7, 7.2, 1.4 Hz, 1H), 5.38 (dd, J = 7.2, 3.7 Hz, 1H), 4.60 (d, A of AB, J = 12.0 Hz, 1H), 4.55 (d, B of AB, J = 12.0 Hz, 1H), 4.53 (s, 2H), 4.06 (dd, J = 5.2, 1.4 Hz, 2H), 3.78 (dd, A of ABX, J = 11.8, 2.9 Hz, 1H), 3.52 (dd, B of ABX, J = 11.8, 5.3 Hz, 1H), 3.15-3.22 (m, 2H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 152.39, 138.07, 137.83, 132.80, 129.09, 128.44, 127.79, 127.70, 125.59, 123.66, 118.84, 103.53, 73.27, 72.40, 69.49, 69.32, 55.47, 54.86.

IR ($CHCl_3$): 3019 (s), 1733 (m), 1525 (m), 1443 (m).

MS (DIP, 20 eV): m/e 459 (M+, 0.1), 252 (1), 181 (3), 149 (1), 119 (7), 108 (2), 107 (5), 93 (3), 92 (12), 91 (100), 81 (2), 40 (7).

**Hept-2-ene-1,7-bisbenzloxy-4,5,6-triol 4,5-carbonate (10).** To a stirred solution of 1.8 g (4.0 mmol) of **9** in 80 mL of ether at -20 °C was added 0.7 mL of $BF_3 \bullet OEt_2$. A precipitate formed immediately. The mixture was stirred at -20 °C for 2 hr, and then 20 mL of 0.5 N $H_2SO_4$ was added (precipitate redissolved). The reaction mixture was allowed to warm to room temperature and the two-phase system was stirred for 5

hr. The aqueous layer was separated and extracted with 50 mL of ether. The combined extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (1:1 hexane/EtOAc) to give 1.4 g (90%) of **10** as a thick syrup. $[\alpha]^{23}_D$ = -30.3°, c = 3.7, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.28 (m, 5H), 6.01 (dt, J = 15.6, 4.7 Hz, 1H), 5.85 (ddt, J = 15.6, 5.8, 1.5 Hz, 1H), 5.18 (t, J = 6.1 Hz,1H), 4.55 (s, 2H), 4.37 (dd, J = 6.4, 5.9 Hz, 1H), 4.05 (d, J = 4.8 Hz, 2H), 3.96 (m, 1H), 3.62 (d, J = 3.3 Hz, 2H), 2.60 (br, 1H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 154.04, 137.99, 137.28, 132.74, 128.52, 128.40, 128.05, 127.83, 127.73, 127.67, 126.55, 80.82, 78.06, 73.80, 72.71, 69.97, 69.79, 69.09.

IR ($CHCl_3$): 1602 (m), 1220 (s), 1071 (m), 769 (m), 735 (m), 671 (m).

MS (DIP, 20 eV): m/e 294 (4), 214 (1), 197 (1), 172 (2), 149 (10), 125 (2), 108 (5), 107 (9), 105 (3), 92 (22), 91 (100), 83 (4), 81 (3), 69 (2), 40 (6).

**Hept-2-ene-1,7-bisbenzloxy-4,5,6-triol (11).** A solution of 90 mg (0.23 mmol) of **10** in 5 mL of MeOH was treated with 20 mg (0.37 mmol) of NaOMe. After 5 hr at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc) to afford 80 mg (97%) of **11** as a thick syrup. $[\alpha]^{23}_D$ = +1.6°, c = 1.4, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.28-7.40 (m, 10 H), 5.80-6.00 (m, 2H), 4.57 (s, 2H), 4.53 (s, 2H), 4.38 (m, 1H), 4.05 (d, J = 4.1 Hz, 2H), 3.90 (m, 1H), 3.60-3.68 (m, 3H), 2.60-3.00 (br, 3H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 138.22, 137.75, 132.26, 128.87, 128.40, 128.29, 127.78, 127.69, 127.52, 74.38, 73.56, 72.30, 71.59, 71.21, 70.88, 70.00.

IR (CHCl3): 3568 (br), 1223 (m), 1217 (m), 1071 (m), 766 (s), 727 (m), 666 (m).

MS (DIP, 20 eV): m/e 250 (0.3), 181 (3), 163 ·7), 160 (4), 149 (3), 131 (1), 108 (2), 107 (8), 96 (5), 92 (16), 91 (100), 73 (3), 70 (8), 40 (20).

**1,4,5,6,7-Pentabenzloxy-hept-2-ene (12).** To a solution of 0.80 g (2.2 mmol) of **11** in 40 mL of THF was added 0.60 g (25 mmol) of NaH, 0.90 mL (7.5 mmol) of BnBr and 20 mg of n-$Bu_4NI$. After 15 hr at room temperature, the reaction mixture was poured into 50 mL of saturated aqueous $NH_4Cl$ and extracted with 100 mL of ether. The ether extract was dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography (5:1 hexane/EtOAc) to give 1.34 g (95%) of **12** as a thick syrup.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.20-7.33 (m, 25 H), 5.77 -5.82 (m, 2H), 4.43-4.65 (m, 10 H), 4.14 (dd, J = 6.9, 4.0 Hz, 1H), 3.98 (d, J = 4.6 Hz, 2H), 3.85 (m, 1H), 3.70-3.76 (m, 3H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 138.93, 138.81, 138.73, 138.46, 130.71, 128.34, 128.25, 128.20, 128.14, 128.02, 127.84, 127.64, 127.52, 127.43, 127.32, 82.02, 79.98, 78.73, 74.68, 73.38, 72.22, 70.82, 70.12, 70.04.

IR ($CHCl_3$): 1218 (s), 780 (m), 756 (m), 670 (m).

MS (DIP, 20 eV): m/e 471 (0.1), 470 (0.3), 253 (2), 197 (2), 181 (5), 163 (4), 149 (1.3), 133 (1.4), 108 (4), 107 (9), 106 (11), 105 (26), 92 (10), 91 (100), 79 (3), 77 (8), 40 (50).

**2,3,4,5-Tetrabenzloxy-D-arabinose (13).** A solution of 0.40 g (0.64 mmol) of **12** in 10 mL of 4:1 $CH_2Cl_2$/MeOH was cooled to -78 °C and treated with excess $O_3$. To the resulting light blue solution was added 5 mL of $Me_2S$ and the mixture was warmed to room temperature. After 6 hr, all volatile components were removed under reduced pressure, and the crude product was purified by flash chromatography (3.5:1 hexanes/EtOAc) to afford 0.316 g (95%) of **13** as a thick syrup. $[\alpha]^{23}_D$ = -2.1°, c = 1, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 9.59 (d, J = 1.4 Hz, 1H), 7.18-7.33 (m, 20 H), 4.66 (d, A of AB, J = 11.8 Hz, 1H), 4.60 (d, A of AB', J = 11.6 Hz, 1H), 4.52 (s, 4H), 4.49 (d, B of AB, J = 11.8 Hz, 1H), 4.34 (d, B of AB', J = 11.6 Hz, 1H), 4.08-4.15 (m, 2H), 3.76-3.85 (m, 2H), 3.67 (dd, J = 10.8, 4.2 Hz, 1H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 201.84, 138.18, 137.72, 137.33, 128.42, 128.33, 128.28, 128.16, 128.04, 127.77, 127.73, 127.58, 84.23, 78.62, 77.65, 74.03, 73.38, 73.30, 72.03, 69.63.

IR ($CHCl_3$): 1732 (m), 1212 (m), 1098 (m), 786 (s), 748 (s), 667 (m).

MS (DIP, 20 eV): m/e 469 (2), 389 (0.8), 297 (3), 181 (7), 106 (18), 91 (100), 40 (45).

**Benzyl Esters (14) and (15).** To a suspension of 4.0 g (25 mmol) of $CrCl_2$ in 40 mL of THF were added 2.6 g (5.0 mmol) of aldehyde **13**, and 2.6 g (10 mmol) of benzyl (α-bromomethyl)-acrylate at ambient temperature. After 1.5 hr, the reaction mixture was poured into 80 mL of saturated aqueous NaCl and extracted with 150 mL of ether. The ether extract was dried ($Na_2SO_4$) and concentrated. The crude product was purified by flash chromatography (20:2:1 hexane/EtOAc/$CHCl_3$). First to elute was 1.7 g (50%) of **15** ($[\alpha]^{23}_D$ = -4.18°, c = 3.2, $CHCl_3$), followed by 1.5 g (44%) of **14** ($[\alpha]^{23}_D$ = -2.01°, c = 1.5, $CHCl_3$).

Benzyl ester **14**:

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.20-7.38 (m, 20H), 6.26 (d, J = 1.3 Hz, 1H), 5.57 (d, J = 0.9 Hz, 1H), 5.18 (s, 2H), 4.71 (d, A of AB, J = 11.5 Hz, 1H), 4.69 (s, 2H), 4.58 (s, 2H), 4.51 (s, 2H), 4.49 (d, B of AB, J = 11.5, 1H), 4.03 (m, 2H), 3.91 (m, 1H), 3.88 (m, 1H), 3.73 (dd, J = 11.2, 6.8 Hz, 1H), 3.63 (dd, J = 5.8, 4.0 Hz, 1H), 2.87 (d, J = 6.0 Hz, 1H), 2.64 (dd, J = 13.3, 2.2 Hz, 1H), 2.35 (dd, J = 13.3, 9.8 Hz, 1H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 167.44, 138.77, 138.59, 138.53, 137.76, 128.54, 128.33, 128.28, 128.13, 128.04, 127.80, 127.69, 127.57, 127.51, 81.85, 79.55, 79.34, 74.09, 73.59, 73.45, 72.41, 70.75, 70.15, 66.59, 36.28.

IR ($CHCl_3$): 1714 (s), 1456 (m), 1145 (m), 1093 (m).

MS (DIP, 20 eV): 471 (0.2), 259 (2), 177 (2), 154 (7), 153 (90), 125 (2.1), 107 (23), 97 (2.5), 91 (100), 79 (8), 40 (56).

Benzyl ester **15**:

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.18-7.48 (m, 20H), 6.22 (d, J = 1.4 Hz, 1H), 5.50 (d, J = 1.0 Hz, 1H), 5.15 (s, 2H), 4.46-4.79 (m, 8H), 3.81-4.02 (m, 4H), 3.71 (dd, J = 9.7, 5.0 Hz, 1H), 3.56 (dd, J = 6.2, 2.5 Hz, 1H), 2.72 (d, J = 7.0 Hz, 1H), 2.56 (dd, J = 9.2, 8.6 Hz, 1H), 9.2, 4.5 Hz, 1H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 167.08, 138.76, 138.61, 138.50, 138.45, 137.67, 136.15, 128.50, 128.29, 128.22, 128.07, 128.00, 127.90, 127.72, 127.66, 127.60, 127.50, 127.43, 127.31, 81.16, 80.00, 79.43, 74.65, 74.21, 73.39, 72.38, 70.20, 70.02, 66.45, 37.17.

IR ($CHCl_3$): 2980 (m), 1711 (m), 1495 (m), 1454 (m), 1210 (s), 1100 (m), 1027 (m).

**t-Butyldimethylsilyl ether (16).** To a stirred solution of alcohol **14** (1.4 g, 2.0 mmol) in 20 mL of DMF was added imidazole (0.83 g, 12 mmol) followed by t-butyldimethylsilyl chloride (1.23 g, 8.16 mmol). After 1 hr at ambient temperature, the reaction mixture was poured into 50 mL of water and extracted with two 100 mL portions of ether. The combined organic layers were dried ($MgSO_4$) and solvent removed under reduced pressure. Flash chromatography (20/1 hexanes/ethyl acetate) gave 1.47 g (90%) of material. $[\alpha]^{23}_D$ = +2.0°, c=2.1, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.22-7.36 (m, 20H), 6.28 (d, J = 1.5 Hz, 1H), 5.66 (d, J = 0.8 Hz, 1H), 5.17 (s, 2H), 4.51-4.92 (m, 8H), 4.14 (m, 1H), 3.97 (m, 1H), 3.78-3.86 (m, 4H), 2.65 (m, 2H), 0.85 (s, 9H), -0.03 (s, 3H), -0.13 (s, 3H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 166.92, 139.42, 139.04, 138.95, 138.46, 137.18, 136.09, 129.06, 128.56, 128.35, 128.20, 128.16, 127.97, 127.74, 127.55, 127.31, 127.28, 84.42, 81.13, 79.15, 77.20, 75.08, 74.79, 73.26, 72.47, 72.05, 69.79, 66.34, 35.40, 25.88, 17.90, -4.30, -5.09.

IR ($CHCl_3$): 3020 (s), 1717 (m), 1151 (m), 1091 (m).

MS (DIP): m/e 801 (m+, 21), 603 (23), 577 (25), 469 (22), 426 (30), 401 (45), 382 (37), 361 (31), 333 (28), 319 (100).

**α-Keto ester (17).** A solution of **16** (1.40 g, 1.75 mmol) in 25 mL of 4/1 methylene chloride/methanol was cooled to -78 °C and treated with excess ozone. The resulting light blue solution was treated with 5 mL of $Me_2S$ and then warmed to ambient temperature. After 6 hr, all volatiles were removed under reduced pressure and the crude residue purified by flash chromatography (12/1 hexanes/ethyl acetate) to afford 1.29 g (92%) of the product. $[\alpha]^{23}_D$ = -0.46°, c = 5, $CHCl_3$.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 7.17-7.37 (m, 20 H), 5.15 (d, A of AB, J = 12.2 Hz, 1H), 5.08 (d, B of AB, J = 12.2 Hz, 1H), 4.41-4.84(m, 8H), 3.67-3.84 (m, 6H), 3.32 (dd, A of ABX, J = 17.1, 8.0 Hz, 1H), 2.97 (dd, B of ABXJ = 17.1, 3.4 Hz, 1H), 0.82 (s, 9H), 0.00 (s, 6H).

$^{13}C$ NMR ($CDCl_3$, 62.9 MHz): δ 192.13, 160.77, 138.78, 138.54, 138.27, 134.69, 129.68, 128.58, 128.50, 128.35, 128.26, 128.17, 127.94, 127.74, 127.64, 127.59, 127.48, 127.35, 83.80, 79.89, 78.65, 74.64, 74.26, 73.32, 71.93, 71.34, 69.18, 67.55, 42.95, 31.45, 26.80, 25.69, 22.50, 20.82, 17.76, 14.04, 13.96, -4.47, -5.18.

IR ($CHCl_3$): 1730 (m), 1221 (s), 1096 (m), 786 (m), 728 (m).

Exact Mass MS (FAB, NOBA): $C_{49}H_{58}O_8Si$
observed: 803.3890 (m+H) calculated: 803.3981 (m+H)

**Pentaacetate of KDO methyl ester (18).** A solution of 250 mg (0.31 mmol) of **17** and 100 mg of 10% Pd/C in 10 mL of MeOH was kept under $H_2$ atmosphere for 24 hr. The solution was filtered and the filtrate was concentrated. The residue was dissolved in 10 mL of 1:1:1 THF-HOAc-$H_2O$ and the mixture was stirred for 6 hr at 50 °C. All volatile components were removed *in vacuo*. The residue was treated with excess anhydrous methanolic ammonia and then concentrated *in vacuo* to provide 50 mg (63%) of crude $NH_4$KDO as a yellow solid. Peracetylation and diazomethane esterification of the crude $NH_4$KDO according to the literature procedure[15] afforded 50 mg (51%) of **18** as a colorless solid.

$^1H$ NMR ($CDCl_3$, 250 MHz): δ 5.39 (m, 1H), 5.32(m, 1H), 5.22 (ddd, J = 9.8 3.9 2.8 Hz), 4.48 (dd, J = 12.3, 2.3 Hz, 1H), 4.17 (d, J= 10.9 Hz, 1H), 4.12 (dd, J = 10.9, 4.0 Hz, 1H), 3.82 (s, 3H), 2.23 (m, 2H), 2.14 (s, 3H), 2.12 (s, 3H), 2.05 (s, 3H), 2.00 (s, 6H).

IR ($CHCl_3$): 1750 (s), 1427 (m), 1220 (m).

MS ((DIP, 20 eV): m/e 373 (0.6), 361 (0.8), 359 (14), 290 (2.8), 289 (21.4), 287 (13.4), 270 (12.5), 245 (21.0), 299.1 (6.0), 228 (25.3), 227 (13.8), 217 (38,6), 187 (44.5), 186 (23.9), 185 (14.1), 175 (6.6), 170 (41.8), 168 (10.6), 157 (34.6), 155 (10.3), 145 (100), 143 (61), 128 (27), 127 (21), 126 (10), 124 (31), 123 (10), 115 (70), 103 (44), 96 44), 97(11), 96 (88), 85 (13), 83 (14), 43 (71).

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