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De Novo Synthesis of L-Colitose and L-Rhodinose Building Blocks

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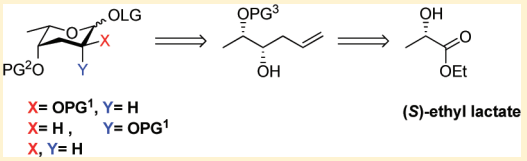
Supporting Information

ABSTRACT: A divergent, practical, and efficient *de novo* synthesis of fully functionalized L-colitose (3,6-dideoxy-L-galactose), 2-*epi*-colitose (3,6-dideoxy-L-talose), and L-rhodinose (2,3,6-trideoxy-L-galactose) building blocks has been achieved using inexpensive, commercially available (*S*)-ethyl lactate as the starting material. The routes center around a diastereoselective Cram-chelated allylation that provides a common homoallylic alcohol intermediate. Oxidation of this common intermediate finally resulted in the synthesis of the three monosaccharide building blocks.



INTRODUCTION

Deoxysugars are commonly found in nature as a component of plants, fungi, and bacteria. One particular class of deoxysugars, the 3,6-dideoxyhexoses, are widespread in the *O*-specific side chain of lipopolysaccharides of Gram-negative bacteria. These sugars serve as antigenic determinants and are vital for bacterial survival. L-Colitose (3,6-dideoxy-L-galactose; Figure 1) is a 3,6-dideoxyhexose of particular interest since this monosaccharide is specific to the *O*-antigen of a large range of Gram-negative bacteria such as *Escherichia coli* O111,[1] *Salmonella enterica*,[2] *Salmonella Adelaide*,[3] *Salmonella greenside*, and *Vibrio cholerae*,[4] which are enteric pathogens responsible for many epidemics. Furthermore, L-colitose is present in the *O*-specific polysaccharides of aerobic heterotrophic marine prokaryotes of the genera *Pseudoalteromonas*.[5] These prokaryotes produce a range of biologically active products such as antibiotics, antitoxins, and antitumor and antiviral agents. To evaluate the immunological properties of L-colitose-containing bacterial oligosaccharides and the potential of the corresponding glycoconjugates as vaccines against bacteria, the development of an efficient synthesis for functionalized L-colitose building blocks remains essential. Previous syntheses of L-colitose building blocks start mainly from expensive L-fucose[6] and/or require many steps.[7] As part of our ongoing program aimed at establishing efficient synthetic pathways for accessing fully protected natural and non-natural monosaccharides,[8] we report a *de novo* synthesis of a L-colitose glycosylating agent starting from inexpensive commercially available (*S*)-ethyl lactate.[9] We extend this synthetic methodology to the preparation of 2-*epi*-colitose (3,6-dideoxy-L-talose) and L-rhodinose (2,3,6-trideoxy-L-galactose), which are closely related to L-colitose (Figure 1).

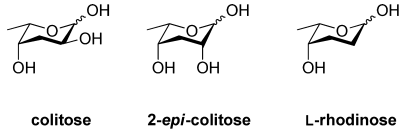
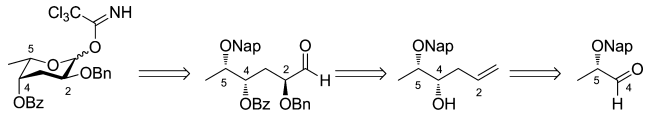


Figure 1. Rare sugar targets.

RESULTS AND DISCUSSION

The retrosynthetic analysis targeted functionalized L-colitose building block **1** (Scheme 1) to be generated from acyclic precursor aldehyde **2**. We envisioned obtaining differentially protected aldehyde **2** via a dihydroxylation/oxidation sequence of homoallylic alcohol **3** that could be obtained by allylation of (*S*)-α-hydroxy aldehyde **4** under Cram-chelation control.[10] Intermediate **4** could be synthesized in two steps starting from (*S*)-ethyl lactate.

Scheme 1. Retrosynthetic Analysis of L-Colitose Building Block 1



2-Naphthylmethyl (Nap) ether protection[11] of the free alcohol in (*S*)-ethyl lactate (**5**), which has the same stereochemistry at C5 as the target L-colitose, followed by reduction of the ester moiety with DIBAL afforded aldehyde **4** in 77% yield over two steps (Scheme 2). Introduction of the remaining L-colitose carbon backbone and the C4 stereocenter was accomplished via Cram-chelated controlled allylation of **4**[12] with allyl trimethyl silane in the presence of $SnCl_4$ in a noncoordinating solvent (DCM).[13] This reaction provided desired homoallylic alcohol **3** (dr = 14:1) in 91% yield. The absolute stereochemistry of the newly formed chiral center was assigned by Mosher ester analysis.[14]

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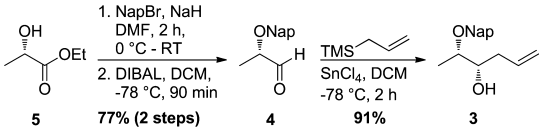
Scheme 2. Synthesis of Homoallylic Alcohol 3

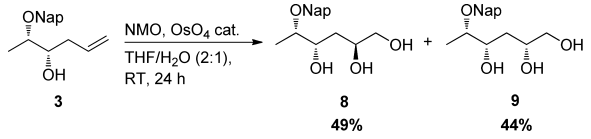


With olefin **3** in hand, we investigated the stereoselective introduction of the C2-OH group using a Sharpless asymmetric dihydroxylation (AD; Table 1).[15] Thus, substrate **3** was treated with the appropriate AD-mix β reagent in *tert*-BuOH/water in order to afford the corresponding 2,4-*anti* intermediate. Surprisingly, the reaction was not stereoselective, and the target triol was obtained as a 1:1 mixture of 2,4-*syn* and 2,4-*anti* diastereoisomers (Table 1, entry 1). The use of AD-mix α, which should favor the formation of 2,4-*syn* triol, also exhibited very low diastereoselectivity (Table 1, entry 2). At least modest diastereoselectivity in line with the selectivity achieved in the Sharpless dihydroxylation reaction of simple terminal olefins[16] was expected.

One strategy that has been used to alter the diastereoselectivity in the Sharpless AD of homoallylic alcohol substrates is to introduce different protecting groups on the homoallylic alcohol. Unfortunately, substrates **6** and **7** containing benzoyl ester and silyl ether protective groups also showed very poor diastereoselectivities ranging from 1:1.3 to 1:2 (Table 1, entries 3–6). The low diastereoselectivity was suspected to be a result of the sterically encumbering C4 and C5 substituents. Thus, it is likely that the substrate cannot fit in the active site of the chiral catalyst and thereby allows for the nonselective dihydroxylation to become the dominant mechanism. Others have reported poor diastereoselectivities for the Sharpless AD of homoallylic alcohol, ether, and ester substrates previously.[17]

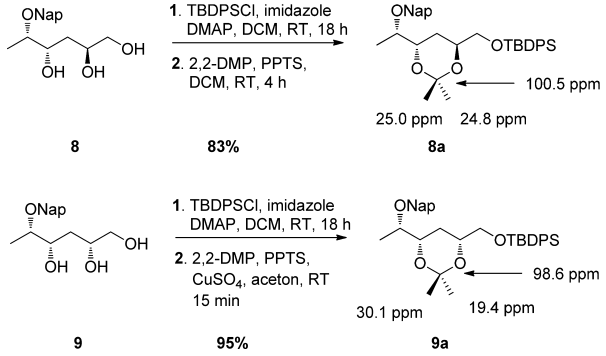
The lack of selectivity when enlisting the Sharpless catalyst prompted us to use the Upjohn dihydroxylation[18] due its lower cost (Scheme 3).[19] Consequently, homoallylic alcohol **3** was treated at room temperature with OsO_4–NMO in tetrahydrofuran/water to furnish an 1:1 mixture of 2,4-*anti* triol **8** and 2,4-*syn* triol **9**. Gratifyingly, **8** and **9** could be separated by silica gel column chromatography to afford triol **8** in 49% yield and diastereoisomer **9** in 44% yield.

Scheme 3. Upjohn Dihydroxylation of Homoallylic Alcohol 3



The absolute configuration of the newly introduced C2-OH was established using Rychnovsky's acetonide method[20] (Scheme 4). Selective protection of the primary alcohol on

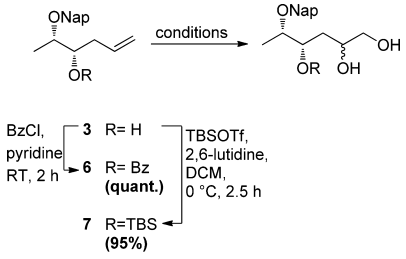
Scheme 4. Synthesis of the C2–C4 Acetonides 8a and 9a



substrate **8** as a TBDPS ether followed by treatment of the intermediate diol with 2,2-DMP in presence of PPTS afforded acetonide **8a**. According to the C13 chemical shifts of the acetonide methyl groups and quaternary carbon, it was determined that **8a** had a 2,4-*anti* configuration. Having established the absolute configuration of C4 through Mosher ester analysis of alcohol **3**, the absolute configuration of C2 in triol **8** was thus determined to be *S*. The same procedure was applied to triol **9** to afford acetonide **9a**. The ^{13}C NMR data was consistent with the assignment of a 2,4-*syn* configuration for **9a** and, thus, an *R*-configured C2 stereocenter.

Having set and defined all the necessary stereocenters in triol **8**, the synthesis of L-colitose **1** was completed (Scheme 5). Strategically, a building block with a C2 nonparticipating protecting group (Bn) was targeted as L-colitose is naturally

Table 1. Survey of Dihydroxylation Attempts



entry	substrate	conditions	dr[a,b]
1	**3**	AD-mix β, *t*BuOH/H_2O (1:1), 0 °C, 12 h	1:1
2	**3**	AD-mix α, *t*BuOH/H_2O (1:1), 0 °C, 12 h	1.5:1
3	**6**	AD-mix β, *t*BuOH/H_2O (1:1), 0 °C, 48 h	2:1
4	**6**	AD-mix α, *t*BuOH/H_2O (1:1), 0 °C, 12 h	2:1
5	**7**	AD-mix β, *t*BuOH/H_2O (1:1), 0 °C, 12 h	1.3:1
6	**7**	AD-mix α, *t*BuOH/H_2O (1:1), 0 °C, 12 h	1.7:1

[a]Ratios determined by ^1H NMR. [b]Major and minor diastereomers of the product mixtures were not determined

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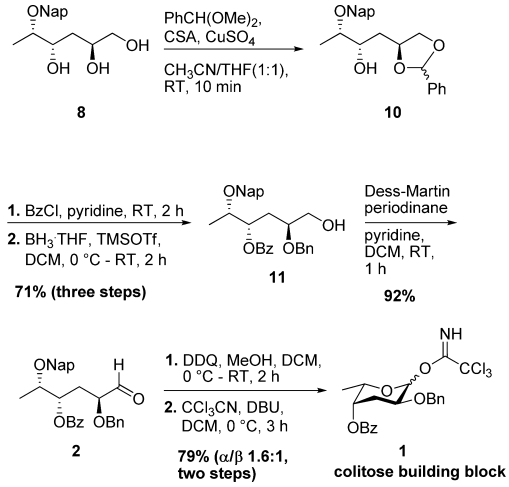
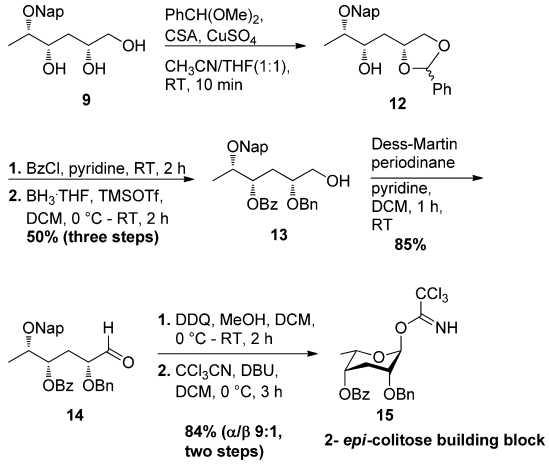
Scheme 5. Synthesis of L-Colitose Building Block 1



only found α-linked to other sugars. An electron-withdrawing protecting group (Bz) was to be placed in the C4 position to stabilize the electron rich deoxysugar building block. Thus, triol **8** was converted selectively to five-membered benzylidene acetal **10**. The remaining hydroxyl group in **10** was benzoylated, and the benzylidene was regioselectively opened using BH_3·THF/TMSOTf to afford primary alcohol **11** in 71% yield over three steps. Although alcohol **11** could not be converted to corresponding aldehyde **2** using Swern[21] or Parikh–Doering[22] conditions, Dess–Martin periodinane[23] provided aldehyde **2** in 92% yield. Removal of the 2-naphthylmethyl protecting group in **2** with DDQ led to the corresponding hemiacetal, which was treated with trichloroacetonitrile in the presence of DBU to give L-colitose trichloroacetimidate **1** as a 1.6:1 α/β mixture in 79% yield over two steps. Coupling constant analysis of the α-anomer ($^3J_{H1,H2}$ = 3.2 Hz) and β-anomer ($^3J_{H1,H2}$ = 7.6 Hz) of imidate **1** are consistent with an axially oriented H2, confirming the C13 acetonide analysis of intermediate **8**.

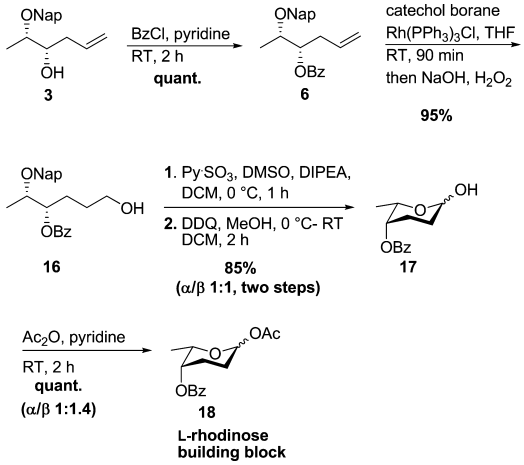
Scheme 6. Synthesis of 2-*epi*-Colitose Building Block 15



As a means to access derivatives of carbohydrates that are not found in nature, the *de novo* approach was applied toward the synthesis of 2-*epi*-colitose building block **15** (Scheme 6). Such non-natural analogues serve as important probes when determining the epitope of oligosaccharide antigens. Thus, 2,4-*syn* triol **9** was converted in three steps to primary alcohol **13** in 50% overall yield. A major undesired byproduct of this reaction sequence was the formation of the C2–C4 six-membered benzylidene acetal.[24] The six-membered ring forms more easily here (in contrast to the conversion of the 2,4-*anti* triol **8** to **10**) due to the formation of a six-membered acetal where all substituents occupy equatorial positions. Oxidation of primary alcohol **13** gave aldehyde **14** in 85% yield. Following 2-naphthylmethyl cleavage in the presence of DDQ, treatment of the intermediate acetal with trichloroacetonitrile and DBU afforded 2-*epi*-colitose trichloroacetimidate **15** in 84% overall yield as a 9:1 α/β mixture. Coupling constant analysis of the major α-anomer ($^3J_{H1,H2}$ < 1.0 Hz) of **15** is consistent with an equatorial-equatorial proton coupling.

L-Rhodinose building block **18** was prepared because of the presence of this motif in different classes of polyketides with antitumor and antibacterial activity[25] (Scheme 7). After

Scheme 7. Synthesis of L-Rhodinose Building Block 18



protection of secondary alcohol **3** as a benzoyl ester, rhodium-catalyzed hydroboration[26] in the presence of catecholborane furnished alcohol **16** in 95% yield over two steps. Parikh–Doering oxidation of alcohol **16** to the corresponding aldehyde followed by cleavage of the 2-naphthylmethyl protecting group in the presence of DDQ and *in situ* cyclization afforded intermediary hemiacetal **17** as an 1:1 α/β anomeric mixture in 85% yield over two steps. Since L-rhodinosyl acetates have been shown to be efficient glycosylating agents,[27] hemiacetal **17** was quantitatively converted into the corresponding glycosylating agent by treatment with acetic anhydride and pyridine. Thus, L-rhodinosyl acetate **18** was prepared in eight steps and 57% overall yield starting from inexpensive (*S*)-ethyl lactate.

■ CONCLUSION

In summary, we have developed a practical synthesis of a fully functionalized L-colitose glycosylating agent in 10 steps with 18% overall yield starting from commercially available (*S*)-ethyl lactate. The divergent route also allowed us to prepare two other congeners of L-colitose: a 2-*epi*-colitose building block (11% overall yield) and a L-rhodinose building block (57% overall yield) from advanced intermediate **3**. The key step of this synthesis is the allylation reaction under Cram-chelated control that introduces the hydroxyl group at C4 in a stereoselective manner. This approach could be extended to

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the preparation of other natural and non-natural 3,6-dideoxy L- and D-hexoses. This methodology will be of particular use for the synthesis of natural products and for the basis of oligosaccharide conjugate vaccines against bacteria that contain the respective glycans on their surface.

EXPERIMENTAL SECTION

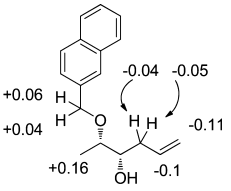
General Experimental Details. Commercial grade reagents and solvents were used without further purification except as indicated below. All reactions were conducted under an Ar atmosphere. The term "concentrated" refers to the removal of solvents and other volatile material using a rotary evaporator while maintaining a water bath temperature under 40 °C. The compounds purified by flash chromatography are further concentrated by the removal of residual solvent under high vacuum (<0.2 mbar). Analytical thin layer chromatography (TLC) was performed on Kieselgel 60 F254 glass plates precoated with a 0.25 mm thickness of silica gel. The TLC plates were visualized with UV light and by staining with Hanessian solution (ceric sulfate and ammonium molybdate in aqueous sulfuric acid) or potassium permanganate solution (potassium permanganate in basic aqueous solution). Column chromatography was performed using Kieselgel 60 (230−400 mesh) silica gel with a typical 50−100:1 weight ratio of silica gel to crude product.

(*S*)-Ethyl 2-(Naphthalen-2-ylmethoxy)propanoate (SI1). At 0 °C, a solution of (*S*)-ethyl lactate (5.0 mL, 44 mmol) and 2-naphthylmethyl bromide (10.6 g, 48 mmol, 1.1 equiv) in DMF (146 mL) was treated with NaH (60% in mineral oil, 1.9 g, 48 mmol). The reaction mixture was stirred at rt for 2 h and quenched by adding ethanol. The reaction was extracted with Et_2O. The combined organic extracts were washed with H_2O and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (cyclohexane/AcOEt = 100:0 to 90:10) to yield the naphthyl ether (10.6 g, 41 mmol, 94%) as a yellow oil: $[\alpha]^{D}_{20}$ −62.6 (*c* 0.96, $CHCl_3$); R_f 0.50 (cyclohexane/AcOEt = 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90−7.77 (m, 4H), 7.54−7.39 (m, 3H), 4.86 (d, *J* = 12.0 Hz, 1H), 4.62 (d, *J* = 12.0 Hz, 1H), 4.28−4.15 (m, 2H), 4.10 (q, *J* = 6.8 Hz, 1H), 1.46 (d, *J* = 6.8 Hz, 3H), 1.30 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 135.2, 133.3, 133.2, 128.3, 128.0, 127.8, 126.9, 126.2, 126.08, 126.07, 74.1, 72.2, 61.0, 18.8, 14.4; IR (thin film) 3055, 2982, 2936, 1742, 1445, 1369, 1270 cm^{-1}; HRMS(ESI) *m*/*z* calcd for $(M + Na)^+$ $C_{16}H_{18}O_3Na$ 281.1154, found 281.1158.

(*S*)-2-(Naphthalen-2-ylmethoxy)propanal (4). To a solution of 2-naphthylmethyl ether **SI1** (8.1 g, 31 mmol) in DCM (314 mL) was added 1 M DIBAL solution in cyclohexane (34.5 mL, 34 mmol) at −78 °C. After 1.5 h the reaction was quenched with methanol (80 mL) and was warmed to rt. A solution of potassium sodium tartrate was added, and the mixture was stirred overnight and extracted with DCM. The combined organic extracts were washed with H_2O, dried over $MgSO_4$, and concentrated. Flash column chromatography (cyclohexane/AcOEt = 100:0 to 90:10) on silica gel gave aldehyde **4** (5.5 g, 25.6 mmol, 82%) as a colorless oil: $[\alpha]^{20}_{D}$ −34.5 (*c* 0.58, $CHCl_3$); R_f 0.75 (toluene/acetone = 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (d, *J* = 1.6 Hz, 1H), 7.93−7.75 (m, 4H), 7.58−7.43 (m, 3H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.76 (d, *J* = 12.0 Hz, 1H), 3.95 (qd, *J* = 6.8, 1.6 Hz, 1H), 1.36 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 134.9, 133.3, 133.2, 128.5, 128.0, 127.8, 127.0, 126.4, 126.2, 125.8, 79.5, 72.2, 15.4; IR (thin film) 3448, 3055, 2980, 2932, 2854, 2801, 2706, 1733, 1602, 1509, 1445, 1373, 1330 cm^{-1}; HRMS(ESI) *m*/*z* calcd for $(M + Na)^+$ $C_{14}H_{14}O_2Na$ 237.0891, found 237.0885.

(2*S*,3*S*)-2-(Naphthalen-2-ylmethoxy)hex-5-en-3-ol (3). $SnCl_4$ (2.6 mL, 23 mmol) was added at −78 °C to a solution of aldehyde **4** (4.4 g, 20 mmol) in DCM (100 mL). After 15 min, allyltrimethylsilane (3.6 mL, 23 mmol) was added, and the mixture was stirred at −78 °C for 2 h, quenched with H_2O, and warmed to rt. The mixture was extracted with DCM, and the combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated. Flash column chromatography on silica gel (hexanes/AcOEt = 90:10) afforded alcohol **3** (4.8 g, 18.7 mmol, 91%) as a colorless oil: $[\alpha]^{20}_{D}$ +39.6 (*c* 0.42, $CHCl_3$); R_f 0.67 (toluene/acetone = 80:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.78 (m, 4H), 7.51−7.45 (m, 3H), 5.93−5.83 (m, 1H), 5.13− 5.07 (m, 2H), 4.83 (d, *J* = 11.6 Hz, 1H), 4.62 (d, *J* = 11.6 Hz, 1H), 3.58−3.54 (m, 1H), 3.53−3.47 (m, 1H), 2.54 (bs, 1H), 2.40−2.34 (m, 1H), 2.26−2.19 (m, 1H), 1.25 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9, 134.9, 133.4, 133.1, 128.4, 128.0, 127.8, 126.6, 126.3, 126.0, 125.9, 117.4, 77.7, 74.4, 71.3, 37.7, 15.6; IR (thin film) 3249, 2976, 2924, 2853, 1670, 1641, 1605, 1509, 1374, 1325 cm^{-1}; HRMS(ESI) *m*/*z* calcd for $(M + Na)^+$ $C_{17}H_{20}O_2Na$ 279.1361, found 279.1358.

The absolute configuration of the C4-hydroxyl group for compound **3** was assigned by ^{1}H NMR analysis of the Mosher ester.



Mosher Ester Analysis (δ*S*-δ*R*)

(4*S*,5*S*)-4-*O*-(Benzoyl)-5-(naphthalen-2-ylmethoxy)hexene (6). A solution of alcohol **3** (827 mg, 3.23 mmol) in pyridine (16 mL) was treated at 0 °C with BzCl (0.75 mL, 6.45 mmol). After 2 h of stirring at rt the mixture was concentrated. The crude was diluted with DCM and washed with HCl, water, and brine. The organic layer was dried over $MgSO_4$ and concentrated. Flash column chromatography (cyclohexane/AcOEt = 100:0 to 70:30) gave benzoate **6** (1.16 g, 3.2 mmol, 100%) as a colorless oil: $[\alpha]^{20}_{D}$ −6.5 (*c* 1, $CHCl_3$); R_f 0.68 (cyclohexane/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.04 (m, 2H), 7.82−7.76 (m, 4H), 7.58−7.54 (m, 1H), 7.46−7.41 (m, 5H), 5.86−5.76 (m, 1H), 5.32−5.27 (m, 1H), 5.11 (dd, *J* = 17.2 Hz, 1.2 Hz, 1H), 5.03 (m, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.70 (d, *J* = 12.0 Hz, 1H), 3.82 (dq, *J* = 1.2, 6.4 Hz, 1H), 2.63−2.57 (m, 1H), 2.53−2.45 (m, 1H), 1.27 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.3, 136.1, 133.9, 133.3, 133.09, 133.04, 130.5, 129.8 (2C), 128.4 (2C), 128.2, 128.0, 127.8, 126.5, 126.1, 125.99, 125.94, 117.9, 75.5, 74.8, 71.4, 34.5, 15.6; IR (thin film) 3059, 2979, 2934, 2867, 1716, 1643, 1602, 1584, 1509, 1491, 1451, 1373, 1349, 1314, 1272 cm^{-1}; HRMS(ESI) *m*/*z* calcd for $(M + Na)^+$ $C_{24}H_{24}O_3Na$ 383.1623, found 383.1598.

(4*S*,5*S*)-4-*O*-(*tert*-Butyldimethylsilyl)-5-(naphthalen-2-ylmethoxy)hexene (7). A solution of alcohol **3** (150 mg, 0.58 mmol) in DCM (6 mL) was treated at 0 °C with 2,6-lutidine (0.14 mL, 1.1 mmol) and TBSOTf (0.2 mL, 0.9 mmol). After 2.5 h, the reaction mixture was quenched with a saturated aq solution of $NaHCO_3$ (20 mL) and extracted with DCM. The combined organic extracts were dried over $MgSO_4$ and concentrated. Flash column chromatography on silica gel (hexanes/AcOEt = 100:0 to 90:10) afforded compound **7** (200 mg, 0.55 mmol, 95%) as a colorless oil: $[\alpha]^{20}_{D}$ +1.4 (*c* 1.0, $CHCl_3$); R_f 0.48 (hexanes/AcOEt = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.71 (m, 4H), 7.48−7.45 (m, 3H), 5.90−5.70 (m, 1H), 5.09−5.00 (m, 2H), 4.76 (d, *J* = 12.0 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 3.80−3.76 (m, 1H), 3.60−3.50 (m, 1H), 2.46−2.39 (m, 1H), 2.19−2.12 (m, 1H), 1.17 (d, *J* = 6.4 Hz, 3H), 0.62 (s, 9H), 0.01 (s, 3H), −0.02 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.6, 136.2, 133.4, 133.0, 128.1, 127.9, 127.8, 126.2, 126.1, 125.9, 125.8, 116.7, 77.5, 74.0, 71.3, 36.5, 26.0 (3C), 18.2, 14.2, −4.33, −4.36; IR (thin film) 3058, 2953, 2926, 2855, 1729, 1642, 1603, 1509, 1462, 1377 cm^{-1}; HRMS(ESI) *m*/*z* calcd for $(M + Na)^+$ $C_{23}H_{34}O_2SiNa$ 393.2226, found 393.2231.

(2*S*,4*S*,5*S*)-5-(Naphthalen-2-ylmethoxy)hexane-1,2,4-triol (8) and (2*R*,4*S*,5*S*)-5-(naphthalen-2-ylmethoxy)hexane-1,2,4-triol (9). At 0 °C, *N*-methylmorpholin-*N*-oxide (2.5 g, 21 mmol) was added to a solution of **3** (2.7 g, 10 mmol) in THF/H_2O (53 mL, 2:1). After 15 min, OsO_4 (2.5 wt % solution in *tert*-butanol, 130 μL, 0.010 mmol) was added, and the mixture was stirred at rt overnight. After dilution with AcOEt, the organic layer was washed with $Na_2S_2O_3$, HCl,

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and water, dried over $MgSO_4$, and concentrated. Flash column chromatography (cyclohexane/AcOEt = 80:20) on silica gel afforded 2,4-*anti* triol **8** (1.5 g, 5.1 mmol, 49%) and the 2,4-*syn* triol **9** (1.3 g, 4.6 mmol, 44%) as white foams.

(2*S*,4*S*,5*S*)-5-(Naphthalen-2-ylmethoxy)hexane-1,2,4-triol (8). $[\alpha]^{20}_D$ +35.2 (*c* 0.45, $CHCl_3$); R_f 0.50 (toluene/acetone = 30:70); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84−7.76 (m, 4H), 7.49−7.38 (m, 3H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 4.01−3.96 (m, 1H), 3.77−3.74 (m, 1H), 3.63 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.54−3.46 (m, 2H), 2.64 (bs, 3H), 1.70 (ddd, *J* = 14.4, 8.8, 3.2 Hz, 1H), 1.57 (ddd, *J* = 14.4, 9.2, 3.6 Hz, 1H), 1.23 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.6, 133.3, 133.1, 128.5, 128.0, 127.8, 126.7, 126.3, 126.1, 125.9, 78.5, 72.5, 71.3, 69.6, 67.0, 35.4, 15.6; IR (thin film) 3372, 3054, 2923, 2871, 1712, 1633, 1602, 1509, 1453, 1401, 1375 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{17}H_{22}O_4Na$ 313.1416, found 313.1435.

(2*R*,4*S*,5*S*)-5-(Naphthalen-2-ylmethoxy)hexane-1,2,4-triol (9). $[\alpha]^{20}_D$ +25.0 (*c* 0.65, $CHCl_3$); R_f 0.59 (toluene/acetone = 30:70); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.77 (m, 4H), 7.51−7.43 (m, 3H), 4.84 (d, *J* = 11.6 Hz, 1H), 4.60 (d, *J* = 11.6 Hz, 1H), 3.99−3.94 (m, 1H), 3.79−3.74 (m, 1H), 3.63 (dd, *J* = 11.2, 3.6 Hz, 1H), 3.52−3.42 (m, 2H), 3.24 (s, 1H), 2.36 (s, 2H), 1.66−1.59 (m, 2H), 1.22 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.5, 133.3, 133.1, 128.5, 128.0, 127.8, 126.7, 126.4, 126.2, 125.9, 78.5, 75.2, 71.8, 71.3, 66.7, 35.3, 15.4; IR (thin film) 3367, 3054, 2923, 2870, 1712, 1633, 1602, 1509, 1449, 1400, 1374 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{17}H_{22}O_4Na$ 313.1416, found 313.1426.

Stereochemical Proof of 8: Synthesis of (2*S*,4*S*,5*S*)-1-(*tert*-Butyldiphenylsilyloxy)-2,4-isopropanedioxy-5-(naphthalen-2-ylmethoxy)-hexane (8a). To a mixture of triol **8** (100 mg, 0.34 mmol), imidazole (28 mg, 0.41 mmol), and DMAP (9 mg, 0.07 mmol) in DCM (3.4 mL) was added TBDPSCl (100 μL, 0.38 mmol). The mixture was stirred for 18 h at rt, then diluted with DCM, washed with a saturated aq solution of NH_4Cl, water, and brine, and dried over $MgSO_4$. Following removal of the solvents *in vacuo*, the crude product was run through a plug of silica gel (hexanes/AcOEt = 100:0 to 70:30) to furnish 180 mg of crude silyl ether. The crude silyl ether dissolved in anhydrous DCM (3.5 mL) was treated with PPTS (17 mg, 0.07 mmol) and 2,2-DMP (220 μL, 1.7 mmol). The mixture was stirred at rt for 4 h and neutralized with an aq saturated solution of $NaHCO_3$. The mixture was extracted with DCM, and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography on silica gel (hexanes/AcOEt = 80:20) gave acetonide **8a** (163 mg, 0.29 mmol, 83%) as a colorless oil: $[\alpha]^D_{20}$ −11.7 (*c* 2.0, $CHCl_3$); R_f 0.23 (hexanes/EtOAc = 90:10); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83−7.80 (m, 4H), 7.71−7.69 (m, 3H), 7.50−7.36 (m, 10H), 4.83 (d, *J* = 12.0 Hz, 1H), 4.79 (d, *J* = 12.0 Hz, 1H), 3.99−3.93 (m, 1H), 3.89−3.86 (m, 1H), 3.74 (dd, *J* = 10.8, 6.0 Hz, 1H), 3.64 (dd, *J* = 10.8, 4.2 Hz, 1H), 3.60−3.54 (m, 1H), 1.74 (ddd, *J* = 15.6, 10.2, 6.6 Hz, 1H), 1.53 (ddd, *J* = 15.6, 9.6, 6.0 Hz, 1H), 1.41 (2s, 6H), 1.18 (d, *J* = 6.6 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 136.7, 135.85 (2C), 135.81 (2C), 133.9, 133.8, 133.4, 133.0, 129.73, 129.71, 128.1, 127.9, 127.8, 127.73 (2C), 127.71 (2C), 126.3, 126.1, 126.0, 125.8, 100.5, 76.4, 71.8, 70.4, 67.9, 66.9, 30.5, 26.9 (3C), 25.0, 24.8, 19.4, 15.6; IR (thin film) 3069, 3051, 2989, 2958, 2930, 2858, 1112 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{36}H_{44}O_4SiNa$ 591.2907, found 591.2894.

Stereochemical Proof of 9: Synthesis of (2*R*,4*S*,5*S*)-1-(*tert*-Butyldiphenylsilyloxy)-2,4-isopropanedioxy-5-(naphthalen-2-ylmethoxy)-hexane (9a). To a mixture of triol **9** (70 mg, 0.24 mmol), imidazole (20 mg, 0.28 mmol), and DMAP (6 mg, 0.05 mmol) in DCM (2.5 mL) was added TBDPSCl (70 μL, 0.26 mmol). The mixture was stirred for 18 h at rt, then diluted with DCM, washed with a saturated aq solution of NH_4Cl, water, and brine, and dried over $MgSO_4$. Following removal of the solvents *in vacuo*, the crude product was run through a plug of silica gel (hexanes/AcOEt = 100:0 to 70:30) to furnish 125 mg of crude silyl ether. The crude silyl ether dissolved in acetone (3.5 mL) was treated with $CuSO_4$ (115 mg, 0.72 mmol), PPTS (12 mg, 0.05 mmol), and 2,2-DMP (150 μL, 1.2 mmol). The mixture was stirred at rt for 10 min, neutralized with an aq saturated solution of $NaHCO_3$, and filtered through Celite. The mixture was extracted with DCM, and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography on silica gel (hexanes/AcOEt = 80:20) gave acetonide **9a** (130 mg, 0.23 mmol, 95%) as a colorless oil: $[\alpha]^D_{20}$ −0.7 (*c* 1.0, $CHCl_3$); R_f 0.23 (hexanes/EtOAc = 90:10); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.80 (m, 4H), 7.72−7.65 (m, 3H), 7.54−7.32 (m, 10H), 4.80 (2d, *J* = 12.4, 12.4 Hz, 2H), 4.01−3.95 (m, 2H), 3.74 (dd, *J* = 10.4, 5.2 Hz, 1H), 3.62−3.52 (m, 2H), 1.59−1.51 (m, 1H), 1.42 (2s, 6H), 1.35−1.26 (m, 1H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.7, 135.8 (3C), 133.8, 133.4, 133.0, 129.75, 129.73, 128.1, 127.9, 127.8, 127.74 (3C), 127.73 (3C), 126.3, 126.1, 126.0, 125.8, 98.6, 77.0, 72.3, 71.9, 69.8, 67.7, 30.1, 28.9, 27.0 (3C), 19.9, 19.4, 15.3; IR (thin film) 3069, 3051, 2989, 2958, 2930, 2858, 1112 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{36}H_{44}O_4SiNa$ 591.2907, found 591.2953.

(2*S*,3*S*)-3-(Naphthalen-2-ylmethoxy)-1-((*S*)-2-phenyl-1,3-dioxolan-4-yl)butan-2-ol (10). Triol **8** (1.30 g, 4.5 mmol), $CuSO_4$ (2.10 g, 14 mmol) and CSA (52 mg, 0.22 mmol) were suspended in CH_3CN/THF (46 mL, 1:1). At 0 °C, benzaldehyde dimethyl acetal (6.7 mL, 45 mmol) was added, and the mixture was stirred for 10 min, neutralized with $NaHCO_3$ and filtered through Celite. The mixture was extracted with DCM and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography on silica gel (hexanes/AcOEt/Et_3N = 80:19:1) gave 1,2-hemiacetal **10** (1.42 g, 3.7 mmol, 83%) as a 9:1 mixture of diastereoisomers: $[\alpha]^{20}_D$ +1.44 (*c* 1.0, $CHCl_3$); R_f 0.25 (hexanes/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.68 (m, 4H), 7.53−7.42 (m, 5H), 7.41−7.33 (m, 3H), 5.82 (s, 1H), 4.84 (d, *J* = 12.0 Hz, 1H), 4.61 (d, *J* = 12.0 Hz, 1H), 4.51−4.48 (m, 1H), 4.18 (dd, *J* = 8.0, 6.8 Hz, 1H), 3.81−3.71 (m, 2H), 3.49−3.43 (m, 1H), 2.65 (dd, *J* = 4.0, 0.8 Hz, 1H), 1.96−1.86 (m, 1H), 1.76 (ddd, *J* = 15.6, 10.4, 5.2 Hz, 1H), 1.24 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.8, 135.6, 133.2, 132.9, 129.2, 128.3 (2C), 128.2, 127.8, 127.7, 126.5 (2C), 126.4, 126.1, 125.9, 125.7, 103.7, 78.3, 75.0, 72.14, 71.10, 70.6, 37.0, 15.5; IR (thin film) 3474, 3053, 2952, 2924, 2874, 1087, 1067 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{24}H_{26}O_4Na$ 401.1729, found 401.1734.

(2*S*,4*S*,5*S*)-5-(Benzyloxy)-6-hydroxy-2-(naphthalen-2-ylmethoxy)hexan-3-yl Benzoate (11). At 0 °C, BzCl (0.8 mL, 6.8 mmol) was added to the solution of hemiacetal **10** (1.3 g, 3.43 mmol) in pyridine (16 mL). The mixture was stirred at rt for 2 h and concentrated. The crude was dissolved in DCM and washed with HCl and water. The organic layer was dried over $MgSO_4$ and concentrated to give the ester. The crude ester in DCM (35 mL) was treated at 0 °C with a 1 M BH_3 solution in THF (10.2 mL, 10.2 mmol). After 15 min TMSOTf (62 μL, 0.34 mmol) was added, and the mixture was warmed slowly at rt. After 1 h, the reaction mixture was cooled to 0 °C, quenched with MeOH (8.5 mL) and Et_3N (0.35 mL), and concentrated. The crude oil was diluted in DCM, washed with water and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography (hexanes/AcOEt = 70:30) on silica gel afforded alcohol **11** (1.4 g, 2.9 mmol, 86% over 2 steps) as a white foam: $[\alpha]^{20}_D$ +29.4 (*c* 1.2, $CHCl_3$); R_f 0.31 (hexanes/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.6 Hz, 2H), 7.81−7.75 (m, 4H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.47−7.41 (m, 5H), 7.37−7.21 (m, 5H), 5.60 (ddd, *J* = 10.4, 4.4, 2.4 Hz, 1H), 4.80 (d, *J* = 12.0 Hz, 1H), 4.71 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 10.8 Hz, 1H), 4.51 (d, *J* = 10.8 Hz, 1H), 3.85−3.76 (m, 2H), 3.63−3.57 (m, 1H), 3.57−3.48 (m, 1H), 2.13 (ddd, *J* = 14.8, 9.2, 2.4 Hz, 1H), 1.94 (dd, *J* = 14.8, 10.4, 3.6 Hz, 1H), 1.79 (bs, 1H), 1.26 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 139.1, 138.2, 133.3, 133.1, 133.0, 130.3, 129.8 (2C), 128.6 (2C), 128.5 (2C), 128.21 (2C), 128.20, 128.0, 127.9, 127.7, 126.5, 126.1, 126.0, 125.9, 76.6, 75.2, 72.8, 72.4, 71.3, 64.4, 32.0, 15.4; IR (thin film) 3470, 3060, 2976, 2927, 2871, 1714, 1621, 1601, 1584, 1509, 1487, 1458, 1450, 1376, 1343 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + H)$^+$ $C_{31}H_{33}O_5$ 485.2328, found 485.2326.

(2*S*,3*S*,5*S*)-5-(Benzyloxy)-2-(naphthalen-2-ylmethoxy)-6-oxohexan-3-yl Benzoate (2). Alcohol **11** (1.00 g, 2.0 mmol), Dess−Martin periodinane (2.63 g, 6.2 mmol), and pyridine (1.7 mL, 20.6

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mmol) in DCM (9 mL) were stirred at rt for 1 h. After addition of a saturated aq solution of $Na_2S_2O_3$ (10 mL) and a saturated aq solution of $NaHCO_3$ (10 mL), the mixture was stirred for additional 15 min. The mixture was extracted with DCM, and the organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated. Flash column chromatography (cyclohexane/AcOEt = 100:0 to 80:20) on silica gel afforded aldehyde **2** (886 mg, 1.84 mmol, 92%) as white foam: $[\alpha]^{20}_D$ −19.4 (*c* 0.64, $CHCl_3$); R_f 0.57 (cyclohexane/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (d, *J* = 2.0 Hz, 1H), 8.06−8.02 (m, 2H), 7.83−7.73 (m, 4H), 7.61−7.55 (m, 1H), 7.48−7.41 (m, 5H), 7.34−7.19 (m, 5H), 5.61 (ddd, *J* = 10.4, 4.4, 2.4 Hz, 1H), 4.79 (d, *J* = 12.4 Hz, 1H), 4.70 (d, *J* = 12.4 Hz, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 4.53 (d, *J* = 11.2 Hz, 1H), 3.89−3.80 (m, 2H), 2.17 (ddd, *J* = 14.4, 10.4, 3.2 Hz, 1H), 2.04 (ddd, *J* = 14.4, 10.4, 2.4 Hz, 1H), 1.17 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.4, 166.1, 137.0, 135.8, 133.38, 133.30, 133.1, 130.0, 129.90 (2C), 128.6 (2C), 128.5 (4C), 128.28, 128.27, 128.0, 127.8, 126.6, 126.1, 126.0, 125.9, 80.6, 74.8, 73.5, 71.5, 71.4, 30.5, 15.3; IR (thin film) 3061, 3032, 2976, 2926, 2864, 2714, 1718, 1601, 1585, 1509, 1495, 1452, 1377 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{31}H_{30}O_5Na$ 505.1991, found 505.1970.

4-*O*-Benzoyl-2-*O*-benzyl-3,6-dideoxy-L-galactohexopyranose (SI2). At 0 °C, DDQ (917 mg, 4.04 mmol) was added to a solution of aldehyde **2** (650 mg, 1.34 mmol) in DCM/MeOH (135 mL, 9:1). The mixture was slowly warmed to rt and stirred for 3 h, then diluted with Et_2O, and quenched with saturated aq solutions of $NaHCO_3$ and $Na_2S_2O_3$. After separation of the layers, the organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated. Flash column chromatography (hexanes/AcOEt = 70:30) on silica gel gave a 1:1 α/β mixture of the target hemiacetal (**SI2**) (383 mg, 1.12 mmol) in 83% yield as a colorless oil: $[\alpha]^{20}_D$ −29.6 (*c* 2.0, $CHCl_3$); R_f 0.28 (hexanes/AcOEt = 60:40); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.03 (m, 4H), 7.61−7.57 (m, 2H), 7.48−7.44 (m, 4H), 7.33−7.24 (m, 10H), 5.35 (d, *J* = 2.8 Hz, 1H, H1-α), 5.24−5.21 (m, 1H, H4-α), 5.19−5.17 (m, 1H, H4-β), 4.78 (2d, *J* = 7.2 Hz, *J* = 11.6 Hz, 2H, H1-β, CH_2Ph-β), 4.70−4.58 (m, 2H, CH_2Ph-β, CH_2Ph-α), 4.55 (d, *J* = 11.6 Hz, 1H, CH_2Ph-α), 4.36 (qd, *J* = 6.4, 1.2 Hz, H5-α), 3.93−3.58 (m, 2H, H5-β, H2-α), 3.57 (ddd, *J* = 5.2, 11.6, 7.6 Hz, 1H, H2-β), 3.08 (bs, 1H, OH-β), 2.85 (bs, 1H, OH-α), 2.45 (ddd, *J* = 14.4, 5.2, 3.2 Hz, 1H, H3-β_{eq}), 2.24 (dddd, *J* = 13.6, 3.6, 4.8, 0.8 Hz, 1H, H3-α_{eq}), 2.15 (ddd, *J* = 13.6, 11.6, 3.2 Hz, 1H, H3-α_{ax}), 1.81 (ddd, *J* = 14.4, 11.6, 3.2 Hz, 1H, H3-β_{ax}), 1.26 (d, *J* = 6.4 Hz, 3H, H6-β), 1.18 (d, *J* = 6.4 Hz, 3H, H6-α); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.1, 166.0, 138.2, 137.6, 133.3, 133.2, 130.1, 129.99, 129.93 (2C), 129.8 (2C), 128.58 (2C), 128.56 (3C), 128.50 (2C), 128.06 (2C), 128.04 (2C), 127.96 (2C), 127.8, 98.9 ($^1J_{C1-H1}$ = 163.9 Hz, C1-β), 91.0 ($^1J_{C1-H1}$ = 175.0 Hz, C1-α), 74.5 (C2-β), 72.8 (C2-α), 72.7 (CH_2-β), 71.6 (C4-α), 71.3 (C4-β), 71.0 (CH_2-α), 70.9 (C5-β), 65.2 (C5-α), 34.0 (C3-β), 28.4 (C3-α), 16.8 (C6-β), 16.5 (C6-α); IR (thin film) 3417, 3064, 3032, 2982, 2937, 2874, 1715, 1267 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{20}H_{22}O_5Na$ 365.1365, found 365.1363.

4-*O*-Benzoyl-2-*O*-benzyl-3,6-dideoxy-L-galactohexopyranosyltrichloroacetimidate (1). At 0 °C, DBU (11 μL, 0.07 mmol) and Cl_3CCN (190 μL, 1.89 mmol) were added to a solution of lactol **SI2** (130 mg, 0.38 mmol) in DCM (1.5 mL). The reaction mixture was stirred for 3 h at 0 °C and concentrated. Flash column chromatography (hexanes/AcOEt/Et_3N = 80:19:1) on silica gel yielded imidate **1** (176 mg, 0.36 mmol) in 95% yield in an α/β ratio of 1.6:1 as a colorless oil: $[\alpha]^{20}_D$ −24.4 (*c* 0.40, $CHCl_3$); R_f **1α** 0.68 (hexanes/AcOEt/Et_3N = 70:29:1); R_f **1β** 0.50 (hexanes/AcOEt/Et_3N = 70:29:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (s, 1H, NH-β), 8.61 (s, 1H, NH-α), 8.08−8.02 (m, 4H), 7.62−7.57 (m, 2H), 7.51−7.45 (m, 4H), 7.31−7.20 (m, 10H), 6.56 (d, *J* = 3.2 Hz, 1H, H1-α), 5.87 (d, *J* = 7.6 Hz, 1H, H1-β), 5.33−5.30 (m, 1H, H4-α), 5.25−5.23 (m, 1H, H4-β), 4.80 (d, *J* = 11.6 Hz, 1H, CH_2-β), 4.67−4.62 (m, 2H, CH_2-α, CH_2-β), 4.57 (d, *J* = 12.0 Hz, 1H, CH_2-α), 4.32 (qd, *J* = 6.8, 2.0 Hz, 1H, H5-α), 4.09−4.03 (m, 2H, H2-α, H5-β), 3.87 (ddd, *J* = 11.2, 7.6, 4.8 Hz, 1H, H2-β), 2.47 (ddd, *J* = 14.4, 4.8, 3.6 Hz, 1H, H3$_{eq}$-β), 2.38−2.27 (m, 2H, H3$_{eq}$-α, H3$_a$-α), 1.96 (ddd, *J* = 14.4, 11.2, 3.6 Hz, 1H, H3$_a$-α), 1.29 (d, *J* = 6.4 Hz, 3H, H6-β), 1.20 (d, *J* = 6.8 Hz, 3H, H6-α); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.1, 165.9, 161.59, 161.57, 138.0, 137.8, 133.42, 133.40, 130.0, 129.9 (2C), 129.8 (4C), 128.66 (3C), 128.61, 128.53 (3C), 128.50, 127.92, 127.90 (2C), 127.8 (2C), 100.1 ($^1J_{C1-H1}$ = 168.1 Hz, C1-β), 94.1 ($^1J_{C1-H1}$ = 178.4 Hz, C1-α), 91.6 (CCl_3), 91.1 (CCl_3), 73.5 (C2-β), 73.0 (CH_2-β), 72.2 (C2-α), 71.3 (CH_2-α), 71.2 (C4-β), 70.7 (C4-α), 70.1 (C5-β), 68.0 (C5-α), 34.0 (C3-β), 29.8 (C3-α), 16.69 (C6-β), 16.62 (C6-α); IR (thin film) 3406, 3344, 2926, 2857, 1718, 1671, 1601, 1497, 1452, 1359 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{22}H_{22}Cl_3NO_5Na$ 508.0461, found 508.0434.

(2*S*,3*S*)-3-(Naphthalen-2-ylmethoxy)-1-((*R*)-2-phenyl-1,3-dioxolan-4-yl)butan-2-ol (12). Using the same procedure as for compound **10**, benzylidene acetal **12** was synthesized starting from triol **9** (1.2 g, 4.1 mmol) in 61% yield as a 1.6:1 diatereoisomeric mixture: $[\alpha]^{20}_D$ +17.0 (*c* 1.0, $CHCl_3$); R_f 0.37 (hexanes/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85−7.78 (m, 8H), 7.50−7.44 (m, 10H), 7.38−7.36 (m, 6H), 5.96 (s, 1H), 5.80 (s, 1H), 4.84 (d, *J* = 11.6 Hz, 2H), 4.63 (d, *J* = 11.6 Hz, 2H), 4.47−4.40 (m, 2H), 4.28 (dd, *J* = 8.0, 6.0 Hz, 1H), 4.13 (dd, *J* = 7.6, 6.8 Hz, 1H), 3.78−3.67 (m, 4H), 3.65−3.59 (m, 2H), 2.99 (d, *J* = 2.4 Hz, 1H), 2.89 (d, *J* = 2.8 Hz, 1H), 2.00−1.80 (m, 4H), 1.27 (2d, *J* = 6.4 Hz, J = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.2, 137.6, 135.89, 135.88, 133.3 (2C), 133.1 (2C), 129.4, 129.2, 128.5 (2C), 128.4 (2C), 128.3 (2C), 127.9 (2C), 127.8 (2C), 126.7, 126.67, 126.66, 126.4 (3C), 126.3 (2C), 126.1 (2C), 125.96, 125.95, 104.2, 103.3, 77.6, 77.4, 75.4, 74.7, 72.9, 71.2 (2C), 70.9 (2C), 70.2, 35.9, 35.5, 15.25, 15.22; IR (thin film) 3496, 3056, 2924, 2871, 1087, 1068 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{24}H_{26}O_4Na$ 401.1729, found 401.1750.

(2*S*,4*S*,5*R*)-5-(Benzyloxy)-6-hydroxy-2-(naphthalen-2-ylmethoxy)hexan-3-yl Benzoate (13). Using the same procedure as for compound **11**, alcohol **13** was synthesized starting from benzylidene acetal **12** (0.90 g, 2.4 mmol) in 82% yield as a white foam: $[\alpha]^{20}_D$ +3.6 (*c* 0.8, $CHCl_3$); R_f 0.25 (cyclohexane/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (m, 2H), 7.85−7.72 (m, 4H), 7.60−7.54 (m, 1H), 7.50−7.40 (m, 5H), 7.26 −7.21 (m, 5H), 5.42−5.35 (m, 1H), 4.81 (d, *J* = 12.0 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.52 (d, *J* = 11.6 Hz, 1H), 4.47 (d, *J* = 11.6 Hz, 1H), 3.85−3.70 (m, 2H), 3.64−3.50 (m, 2H), 2.17−2.08 (m, 2H), 1.87 (bs, 1H), 1.24 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 138.1, 135.9, 133.3, 133.19, 133.10, 130.2, 129.8 (2C), 128.5 (4C), 128.2, 128.0, 127.9 (2C), 127.85, 127.81, 126.6, 126.2, 126.03, 126.02, 76.7, 74.7, 73.0, 71.3, 71.2, 63.7, 30.7, 15.3; IR (thin film) 3469, 3060, 2926, 2871, 1714, 1602, 1584, 1509, 1495, 1451, 1375, 1345 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na)$^+$ $C_{31}H_{32}O_5Na$ 507.2147, found 507.2164.

(2*S*,3*S*,5*R*)-5-(Benzyloxy)-2-(naphthalen-2-ylmethoxy)-6-oxohexan-3-yl Benzoate (14). Using the same procedure as for compound **2**, aldehyde **14** was synthesized starting from alcohol **13** (720 mg, 1.48 mmol) in 85% yield as white foam: $[\alpha]^{20}_D$ +4.0 (*c* 0.62, $CHCl_3$); R_f 0.53 (cyclohexane/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 1.2 Hz, 1H), 8.06−7.95 (m, 2H), 7.87−7.70 (m, 4H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.47−7.38 (m, 5H), 7.23−7.19 (m, 5H), 5.54−5.50 (m, 1H), 4.78 (d, *J* = 12.0 Hz, 1H), 4.65 (d, *J* = 12.0 Hz, 1H), 4.56 (d, *J* = 11.6 Hz, 1H), 4.44 (d, *J* = 11.6 Hz, 1H), 3.86 (td, *J* = 5.6, 1.2 Hz, 1H), 3.78−3.72 (m, 1H), 2.29 (ddd, *J* = 14.8, 5.6, 4.4 Hz, 1H), 2.17 (ddd, *J* = 14.8, 8.8, 5.6 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 165.8, 137.1, 135.8, 133.3, 133.2, 133.1, 130.12, 129.8 (2C), 128.6 (2C), 128.5 (2C), 128.3, 128.14, 128.12 (2C), 128.0, 127.8, 126.6, 126.2, 126.04, 126.02, 80.5, 74.1, 72.4, 71.8, 71.3, 30.3, 15.0; IR (thin film) 3061, 2978, 2930, 2866, 2714, 1718, 1601, 1584, 1509, 1495, 1452, 1377, 1338 cm^{-1}; HRMS(ESI) *m*/*z* calcd for (M + Na + MeOH)$^+$ $C_{32}H_{34}O_6Na$ 537.2253, found 537.2243.

4-*O*-Benzoyl-2-*O*-benzyl-3,6-dideoxy-L-talohexopyranose (SI3). At 0 °C, DDQ (520 mg, 2.3 mmol) was added to a solution of aldehyde **14** (370 mg, 0.76 mmol) in DCM/MeOH (76 mL, 9:1). The mixture was slowly warmed to rt and stirred for 3 h, then diluted with Et_2O, and quenched with $NaHCO_3$ and $Na_2S_2O_3$. After separation of the layers, the organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated. Flash column chromatography (hexanes/AcOEt = 70:30) on silica gel gave a 1:1 α/β mixture of hemiacetal **SI3** (247 mg,

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0.72 mmol) in 94% yield as a colorless oil: $[\alpha]^{20}_{D}$ −49.9 (*c* 1.0, $CHCl_3$); R_f 0.28 (hexanes/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16−8.12 (m, 4H), 7.61−7.54 (m, 2H), 7.45−7.35 (m, 4H), 7.27−7.18 (m, 10H), 5.43 (s, 1H, H1-α), 5.13−5.10 (m, 1H, H4-α), 5.05−5.03 (m, 1H, H4-β), 4.91−4.80 (dd, J = 12.4 Hz, J < 1.0 Hz, 1H, H1-β), 4.64 (d, J = 11.6 Hz, 1H, CH_2-β), 4.58 (d, J = 11.6 Hz, 1H, CH_2-α), 4.54 (d, J = 11.6 Hz, 1H, CH_2-α), 4.47 (qd, J = 6.4, 1.6 Hz, 1H, H5-α), 4.42 (d, J = 11.6 Hz, 1H, CH_2-β), 4.26 (d, J = 12.4 Hz, 1H, OH-β), 3.95 (qd, J = 6.4, 1.6 Hz, 1H, H5-β), 3.65−3.63 (m, 1H, H2-β), 3.56−3.54 (m, 1H, H2-α), 3.15 (bs, 1H, OH-α), 2.74 (adt, J = 16.0, 2.4 Hz, 1H, H3-β_{eq}), 2.41 (adtd, J = 15.4, 3.2, 1.2 Hz, 1H, H3-α_{eq}), 2.24 (adt, J = 15.4, 3.6 Hz, 1H, H3-α_{ax}), 1.91 (adt, J = 16.0, 3.6 Hz, 1H, H3-β_{ax}), 1.36 (d, J = 6.4 Hz, 3H, H6-β), 1.30 (d, J = 6.4 Hz, 3H, H6-α); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.63, 166.61, 138.0, 137.2, 133.1, 132.9, 130.3, 130.1, 130.08 (2C), 130.04 (2C), 128.4 (4C), 128.39 (2C), 128.32 (2C), 128.1 (2C), 127.9, 127.8 (2C), 127.5, 94.7 ($^1J_{C1-H1}$ = 164.8 Hz, C1-β), 93.1 ($^1J_{C1-H1}$ = 173.7 Hz, C1-α), 72.9 (C5-β), 71.9 (C2-β), 71.7 (C2-α), 71.5 (CH_2-β), 71.1 (CH_2-α), 68.7 (C4-α), 67.7 (C4-β), 65.2 (C5-α), 29.6 (C3-β), 26.4 (C3-α), 17.2 (C6-β), 16.8 (C6-α); IR (thin film) 3427, 3064, 3032, 2982, 2936, 2874, 1709, 1271, 1068 cm^{-1}; HRMS(ESI) m/z calcd for (M + Na)$^+$ $C_{20}H_{22}O_5Na$ 365.1365, found 365.1387.

4-*O*-Benzoyl-2-*O*-benzyl-3,6-dideoxy-L-talohexopyranosyl-trichloroacetimidate (15). At 0 °C, DBU (9 μL, 0.06 mmol) and Cl_3CCN (146 μL, 1.46 mmol) were added to a solution of lactol **SI3** (100 mg, 0.29 mmol) in DCM (1.1 mL). The reaction mixture was stirred for 3 h at 0 °C and concentrated. Flash column chromatography (hexanes/AcOEt/Et_3N = 80:19:1) on silica gel yielded imidate **15** (127 mg, 0.26 mmol) in 89% yield in an α/β ratio of 9:1 as a colorless oil: $[\alpha]^{20}_{D}$ −31.4 (*c* 0.75, $CHCl_3$); R_f 0.56 (hexanes/AcOEt/Et_3N = 70:29:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (s, 1H, NH), 8.03−7.96 (m, 2H), 7.49−7.41 (m, 1H), 7.30−7.21 (m, 2H), 7.19−7.09 (m, 5H), 6.39 (s, 1H, H1), 5.06−5.04 (m, 1H, H4), 4.56 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.48 (d, J = 11.6 Hz, 1H, CH_2Ph), 4.30 (qd, J = 6.8, 1.6 Hz, 1H, H5), 3.63−3.61 (m, 1H, H2), 2.40 (dddd, J = 15.6, 3.2, 2.8, 1.6 Hz, 1H, $H3_{eq}$), 2.17 (ddd, J = 15.6, 4.0, 3.6 Hz, 1H, $H3_a$), 1.21 (d, J = 6.8 Hz, 3H, H6); ^{13}C NMR (151 MHz, $CDCl_3$) δ 166.6, 160.6, 137.8, 133.0, 130.2, 130.0 (2C), 128.4 (2C), 128.3 (2C), 127.7 (2C), 127.6, 96.3 ($^1J_{C1-H1}$ = 180.9 Hz, C1), 90.9 (CCl_3), 71.5 (C4), 70.0 (C5), 68.1 (C2), 67.9 (CH_2), 27.5 (C3), 16.9 (C6); IR (thin film) 3336, 2925, 2854, 1715, 1670, 1602, 1492, 1452, 1366 cm^{-1}; HRMS(ESI) m/z calcd for (M + Na)$^+$ $C_{22}H_{22}Cl_3NO_5Na$ 508.0461, found 508.0434.

(2*S*,3*S*)-6-Hydroxy-2-(naphthalen-2-ylmethoxy)hexan-3-yl Benzoate (16). A solution of alkene **6** (620 mg, 1.72 mmol) and $Rh(PPh_3)_3Cl$ (56 mg, 0.06 mmol) in THF (14 mL) was cooled to 0 °C. Catecholborane 1 M in THF (5.1 mL, 5.1 mmol) was added and the reaction was stirred at 0 °C for 3 h. After dilution with THF/MeOH (7 mL, 1:1) and addition of 3 M solution of NaOH (4 mL) and an aq solution 35% H_2O_2 (4 mL), the reaction was stirred overnight and quenched with a saturated solution of Na_2SO_3 (10 mL). After dilution with Et_2O, the organic layer was washed with $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated. Flash column chromatography (cyclohexane/AcOEt/Et_3N = 80:19:1) on silica gel afforded alcohol **16** (620 mg, 1.63 mmol, 95%) as a colorless oil: $[\alpha]^{20}_{D}$ −5.2 (*c* 1.0, $CHCl_3$); R_f 0.28 (cyclohexane/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07−8.04 (m, 2H), 7.81−7.75 (m, 4H), 7.58−7.54 (m, 1H), 7.47−7.42 (m, 5H), 5.31−7.27 (m, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 3.83−3.77 (m, 1H), 3.66 (t, J = 6.4 Hz, 2H), 3.37−3.83 (m, 1H), 1.94−1.77 (m, 2H), 1.69−1.54 (m, 2H), 1.27 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 136.0, 133.3, 133.1, 133.0, 130.4, 129.8 (2C), 128.5 (2C), 128.2, 128.0, 127.8, 126.5, 126.1, 126.0, 125.9, 76.0, 75.1, 71.4, 62.7, 28.8, 26.1, 15.5; IR (thin film) 3422, 3058, 2952, 2933, 2870, 1715, 1601, 1584, 1450, 1376, 1341 cm^{-1}; HRMS(ESI) m/z calcd for (M + Na)$^+$ $C_{24}H_{26}O_4Na$ 401.1729, found 401.1737.

(2*S*,3*S*)-2-(Naphthalen-2-ylmethoxy)-6-oxohexan-3-yl Benzoate (SI4). To a solution of alcohol **16** (450 mg, 1.19 mmol), DIPEA (1 mL, 5.9 mmol) and DMSO (0.8 mL, 11.9 mmol) in DCM (6 mL) at 0 °C was added SO_3·pyridine complex (568 mg, 3.60 mmol). After 1 h, the reaction mixture was quenched with a saturated aq solution of $Na_2S_2O_3$ (12 mL) and warmed to rt. The aq layer was extracted with DCM. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash column chromatography (hexanes/AcOEt = 80:20) on silica gel afforded aldehyde **SI4** (439 mg, 1.16 mmol, 98%) as a colorless oil: $[\alpha]^{20}_{D}$ −2.1 (*c* 0.80, $CHCl_3$); R_f 0.44 (hexanes/EtOAc = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 8.04 (d, J = 7.2 Hz, 2H), 7.85−7.72 (m, 4H), 7.58 (t, J = 7.2 Hz, 1H), 7.47 −7.42 (m, 5H), 5.34−5.23 (m, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.69 (d, J = 12.0 Hz, 1H), 3.83−3.77 (m, 1H), 2.53 (t, J = 7.6 Hz, 2H), 2.20−2.03 (m, 2H), 1.28 (d, J = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.3, 166.3, 135.9, 133.36, 133.30, 133.1, 130.09, 129.8 (2C), 128.5 (2C), 128.2, 128.0, 127.8, 126.6, 126.2, 126.0, 125.9, 75.2, 75.0, 71.4, 40.3, 22.3, 15.3; IR (thin film) 3057, 2935, 2976, 2863, 2735, 1716, 1271 cm^{-1}; HRMS(ESI) m/z calcd for (M + Na)$^+$ $C_{24}H_{24}O_4Na$ 399.1572, found 399.1565.

4-*O*-Benzoyl-2,3,6-trideoxy-L-galactohexopyranose (17). At 0 °C, DDQ (760 mg, 3.30 mmol) was added to a solution of aldehyde **SI4** (439 mg, 1.10 mmol) in DCM/MeOH (22 mL, 9:1). The mixture was slowly warmed to rt, stirred for 3 h, diluted with Et_2O, and quenched with a saturated aq solution of $NaHCO_3$ and a saturated aq solution of $Na_2S_2O_3$. After separation of the layers, the organic layer was washed with H_2O, dried over $MgSO_4$, and concentrated. Flash column chromatography (hexanes/AcOEt = 70:30) on silica gel gave an inseparable 1:1 α/β mixture of hemiacetal **17** (230 mg, 0.97 mmol) in 87% yield as a colorless oil: $[\alpha]^{20}_{D}$ −14.7 (*c* 1.0, $CHCl_3$); R_f 0.45 (hexanes/AcOEt = 50:50); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.10 (m, 4H), 7.60−7.55 (m, 2H), 7.47−7.43 (m, 4H), 5.42 (d, J = 2.4 Hz, 1H, H1-α), 5.09−5.07 (m, 1H, H4-α), 5.01−4.98 (m, 1H, H4-β), 4.88 (dd, J = 9.2, 2.4 Hz, 1H, H1-β), 4.38 (qd, J = 6.4, 1.2 Hz, 1H, H5-α), 3.87 (qd, J = 6.4, 1.2 Hz, 1H, H5-β), 3.15 (bs, 1H, OH-β), 2.66 (bs, 1H, OH-α), 2.31−2.14 (m, 2H, H3-α, H3-β), 2.08−1.61 (m, 6H, H2-α, H3-α, H3-β, H2-β, H2-β, H2-α), 1.27 (d, J = 6.4 Hz, 3H, H6-β), 1.18 (d, J = 6.4 Hz, 3H, H6-α); ^{13}C NMR (101 MHz, $CDCl_3$) 166.31, 166.30, 133.2, 133.1, 130.4, 130.2, 129.9 (2C), 129.8 (2C), 128.55 (2C), 128.54 (2C), 96.3 (C1-β), 91.8 (C1-α), 73.1 (C5-β), 70.1 (C4-α), 68.7 (C4-β), 65.4 (C5-α), 27.8 (C2-β), 27.4 (C3-β), 24.4 (C2-α), 22.4 (C3-α), 17.48 (C6-β), 17.47 (C6-α); IR (thin film) 3416, 3064, 2980, 2938, 2863, 1715, 1601, 1584, 1450, 1384, 1358 cm^{-1}; HRMS(ESI) m/z calcd for (M + Na)$^+$ $C_{13}H_{16}O_4Na$ 259.0946, found 259.0983.

1-*O*-Acetyl-4-*O*-benzoyl-L-rhodinopyranose (18). Ac_2O (3.4 mL, 36 mmol) was added at 0 °C to a solution of hemiacetal **17** (172 mg, 0.72 mmol) in pyridine (6 mL). The mixture was stirred at rt for 2 h, and the solvents were removed. The crude product was coevaporated with toluene to give quantitatively rhodinosyl acetate **18** (200 mg, 0.72 mmol) as an oil in an α/β ratio of 41:59: $[\alpha]^{20}_{D}$ −8.4 (*c* 0.95, $CHCl_3$); R_f 0.28 (hexanes/AcOEt = 70:30); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.09 (m, 4H), 7.60−7.56 (m, 2H), 7.48−7.44 (m, 4H), 6.25 (s, 1H, H1-α), 5.80 (dd, J = 9.6, 2.4 Hz, 1H, H1-β), 5.11 (as, 1H, H4-α), 5.03 (ad, J = 1.6 Hz, 1H, H4-β), 4.22 (qd, J = 6.4, 1.2 Hz, 1H, H5-α), 3.97 (qd, J = 6.4, 1.6 Hz, 1H, H5-β), 2.27−2.19 (m, 1H, H3-β), 2.15 (s, 3H, CH_3CO-β), 2.13 (s, 3H, CH_3CO-α), 2.08−1.99 (m, 2H, H2-α, H3-α), 1.96−1.85 (m, 3H, H3-α, H2-β, H3-β), 1.79−1.72 (m, 1H, H2-β), 1.68−1.65 (m, 1H, H2-α), 1.28 (d, J = 6.4 Hz, 3H, H6-β), 1.20 (d, J = 6.4 Hz, 3H, H6-α); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.8, 169.5, 166.2, 166.2, 133.3, 133.2, 130.2, 130.1, 129.9 (2C), 129.8 (2C), 128.6 (2C), 128.5 (2C), 94.4 ($^1J_{C1-H1}$ = 161.7 Hz, C1-β), 92.1 ($^1J_{C1-H1}$ = 177.5 Hz, C1-α), 73.9 (C5-β), 69.4 (C4-α), 68.5 (C4-β), 67.8 (C5-α), 27.1 (C3-β), 25.0 (C2-β), 23.2 (C2-α), 22.8 (C3-α), 21.4 (2C, CH_3CO), 17.4 (C6-α), 17.3 (C6-β); IR (thin film) 3064, 2983, 2963, 2939, 2868, 1745, 1714, 1601, 1584, 1491, 1450, 1366, 1329 cm^{-1}; HRMS(ESI) m/z calcd for (M + Na)$^+$ $C_{15}H_{18}O_5Na$ 301.1052, found 301.1064.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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