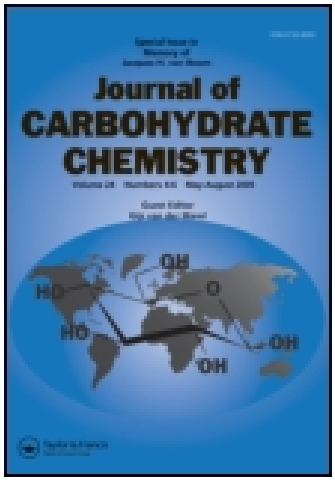

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Efficient Synthesis of Direct Precursors of the Carbohydrate Moiety of New Antibacterials 6-Epi-VIC-105555 and 6-Epi-VIC-II

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In search for new antibiotics we have developed a novel route leading to direct precursors of the carbohydrate moieties of new promising antibacterial agents 6-epi-VIC-105555 and 6-epi-VIC-II. The presented synthetic strategy consists of using as starting material the readily available β-dibenzylamino-α-ketoester and application of a sequence of chemical transformations on C-7: olefination or methylation, reduction, deoxygenation of the terminal alcohol, and finally hydrogenation. The desired molecules were obtained in a stereoselective fashion and with good overall yields.

Keywords Lincosamides; Antibacterials; Stereoselective synthesis; Azetidinium salt; Darzens condensation

INTRODUCTION

Lincomycin **1**[1] and its semisynthetic congener clindamycin **2**[2] (Fig. 1) are the most representative examples of the lincosamide class of antibacterial agents and are used therapeutically for the treatment of mixed anaerobic and aerobic infections, and additionally as an alternative in the treatment of patients allergic to β-lactam antibiotics.[3] Lincosamides exert their antibacterial activity by

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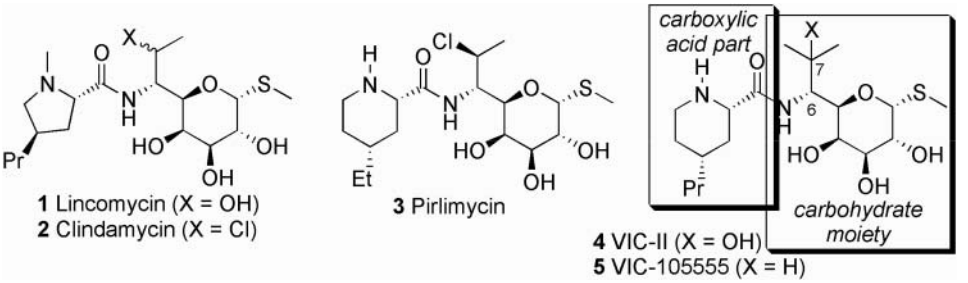


Figure 1: Structures of known lincosamide antibacterials.

binding to the ribosome and inhibiting bacterial protein synthesis.[4] Despite the success of the compounds **1** and **2**, finding second-generation lincosamides with an extended antibacterial spectrum (including enterococci,[5] methicillin-resistant *Staphylococcus aureus*, and clindamycin-resistant strains), an improved side effect profile (coverage of *Clostridium difficile* to prohibit pseudomembranous colitis),[6] and superior pharmacokinetics (once-daily dosing) is still desirable. For that reason several methods for semisynthetic modification of lincomycin **1** and clindamycin **2** have been reported; for example, increasing the amino acid ring size from pyrrolidine (five membered) to piperidine (six membered) has resulted in a potent veterinary antibiotic pirlimycin **3**,[7] and most recently substitution of the 7-hydroxy group by a methyl group in conjunction with novel amides resulted in the discovery of VIC-II **4** and structurally similar VIC-105555 **5** (Fig. 1), both compounds showing a very promising antibacterial activity.[8] The latter has been rapidly progressed into preclinical development.

Synthetic work on the preparation of the antibacterial agents **1–5** has mainly been focused on the preparation of the carbohydrate moiety (Fig. 1) that represents the principal difficulty of the steric control in introducing two chiral centers at C-6 and C-7 in the case of **1–3** and one chiral center at C-6 in the case of **4–5**.[9] Coupling with the appropriate carboxylic acid fragment and introduction of the glycoside thiomethyl group can be considered as solved.[7,8,10]

As a part of our program aimed at developing new versatile procedures for carbohydrate synthesis, we became interested in preparing the precursors of the sugar moiety of the VIC-II **4** and VIC-105555 **5**, in light of the importance of those compounds for development of new antibiotics. We have previously reported on several applications of dihalogenoacetate carbanions[11] and developed a general synthesis of α-ketoesters from carbonyl compounds using potassium alkyl dichloroacetates.[12] Applied to dialdosugar derivatives, the method proved to be very convenient for the chain extension with an α-ketoester unit[13] and to introduce a functionality at the C-6 position.[14] In this report we describe a successful application of this protocol for the stereoselective

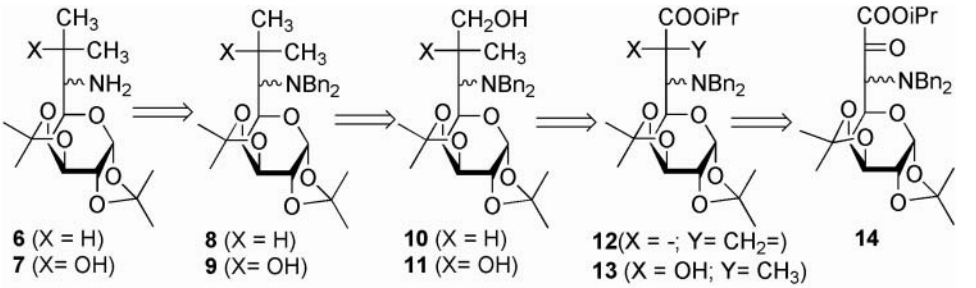


Figure 2: Retrosynthetic analysis.

synthesis of the direct precursors of the carbohydrate moiety of new antibacterial agents, 6-epi-VIC-II **4** and 6-epi-VIC-105555 **5**.

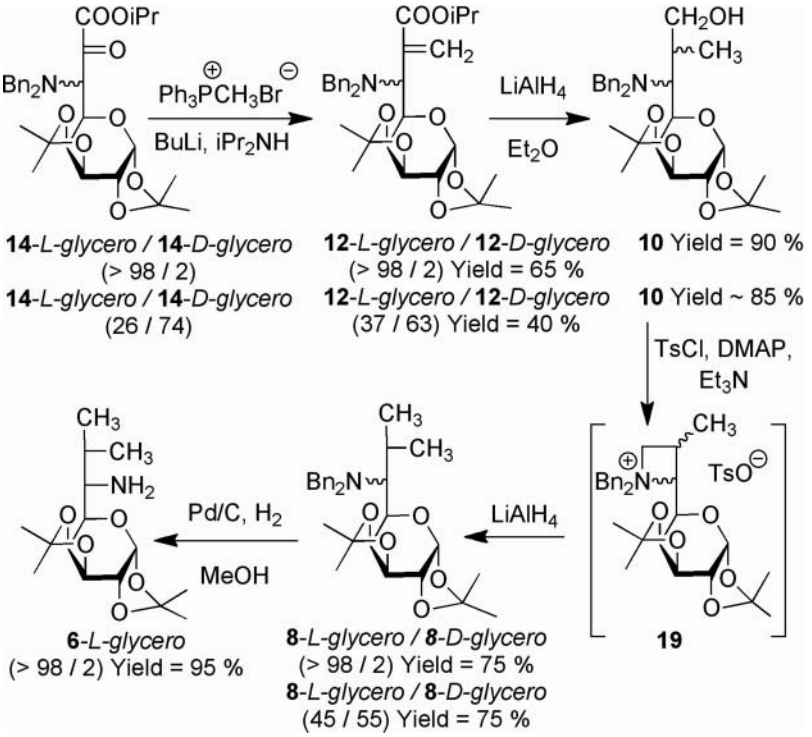
RESULTS AND DISCUSSION

Our synthetic strategy leading stereoselectively to compounds **6**, precursors of the carbohydrate fragments of antibiotic 6-epi-VIC-105555, and to the molecule **7**, the sugar fragment of the C-6 epimer of VIC-II, is presented in Figure 2. In the case of the synthesis of carbohydrate **6**, the synthetic strategy consists of using as starting material the readily available β-dibenzylamino-α-ketoester **14** and application of a sequence of chemical transformations: carbonyl olefination; complete reduction of a bifunctional α, β-ethylenic ester; deoxygenation of the terminal alcohol; and finally hydrogenolysis to yield selectively the desired molecule. A similar strategy can be applied for the preparation of the carbohydrate **7**, the main difference being the C—C bond formation by regioselective methylation of the ketone unit of the starting material **14** in the first step of the synthesis. The β-dibenzylamino-α-ketoester **14** was chosen as the starting material as it can be easily synthesized as a mixture of two epimers, that is, **14**-$_{D}$-*glycero* or **14**-$_{L}$-*glycero*. From this mixture epimer **14**-$_{D}$-*glycero* can be isolated in pure form, although the separation is difficult.[15] In this study, therefore, we use **14**-$_{L}$-*glycero* as starting material, as this epimer can be much more easily obtained. Additionally, in the preparation of precursor of the carbohydrate moiety of 6-epi-VIC-105555, mixture **14**-$_{L}$-*glycero*/**14**-$_{D}$-*glycero* is also tested.

Synthesis of the Direct Precursors of the Carbohydrate Moiety of 6-epi-VIC-105555

The detailed synthetic pathway leading selectively to the precursors of the carbohydrate moiety of 6-epi-VIC-105555 is presented in Scheme 1.

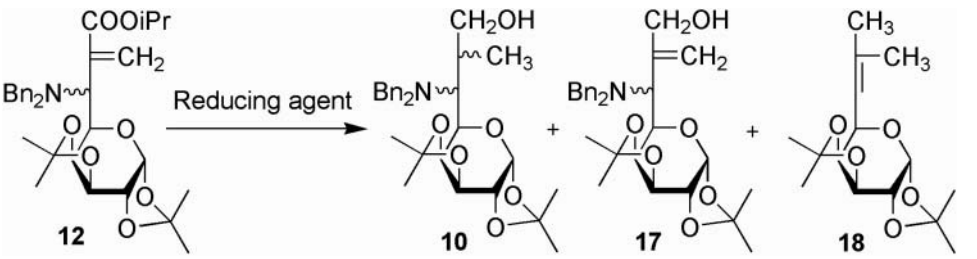
The first step of the reaction sequence is the carbonyl olefination reaction of β-dibenzylamino-α-ketoester **14** with methyltriphenylphosphonium bromide and LDA as a base.[16] In the case of epimer **14**-$_{L}$-*glycero,* ^{1}H NMR, ^{13}C



Scheme 1: Preparation of the precursors of the carbohydrate moiety of 6-epi-VIC-105555.

NMR, and X-ray analyses of the so-obtained olefin **12**-$_L$-*glycero* unambiguously demonstrated the configurational integrity of the chiral center at C-6.[17] When the reaction was performed using an epimeric mixture **14**-$_L$-*glycero* / **14**-$_D$-*glycero,* the lower reactivity of **14**-$_D$-*glycero* compared with its C-6 epimer was observed, and that accounts for the lower yield of the reaction. Next, several attempts to reduce the ester moiety of the olefin **12** with different reducing agents were performed (Table 1) with the aim to obtain the compound **17**. In the case of the use of DIBAL[18] (Table 1, entry 1) or AlH_3,[19] generated in situ by addition of $LiAlH_4$ to $AlCl_3$ (Table 1, entry 2), the desired alcohol **17** was isolated with low yields and gave predominantly the olefin **18**, resulting from 1,4 addition followed by the elimination of the amino group. In turn, when $LiAlH_4$ was used as reducing agent (Table 1, entries 3–6), unexpectedly but luckily for us, simultaneous reduction of both ester function and C=C double bond was noted, and amino alcohol **10** was isolated as the major product. The reaction worked equally well for both, the pure epimer **12**-$_L$-*glycero* (Table 1, entries 3 and 4) and the mixture of epimers **12**-$_L$-*glycero*/**12**-$_D$-*gycero* (Table 1, entries 5 and 6). It has to be noted that this transformation generates a second chiral center on the C-7 carbon; however, since this center disappears in the

Table 1: Reduction of the olefine **12** using different reducing agents



Entry	**12**[a]	Reducing agent	**10**[a]/ Yield (%)[b]	**17**[a]/ Yield (%)[b]	**18**/ Yield (%)[b]
1	**12**-*L-glycero*	DIBAL	—	**17**-*L-glycero*/11	55
2	**12**-*L-glycero*	$LiAlH_4/AlCl_3$	—	**17**-*L-glycero*/37	63
3	**12**-*L-glycero*	$LiAlH_4$, 1.3 equiv.	**10**/64	—	36
4	**12**-*L-glycero*	$LiAlH_4$, 1.8 equiv.	**10**/90	—	10
5	**12**-*L-glycero*/**12**-*D-glycero* (46/54)	$LiAlH_4$, 1.6 equiv.	**10** / 92	—	—
6	**12**-*L-glycero*/**12**-*D-glycero* (40/60)	$LiAlH_4$, 1.6 equiv.	**10** / 85	—	—

[a]Epimeric ratio determined by ^{1}H NMR of the crude reaction mixture.
[b]Yield of isolated product.

next step we did not attempt to establish its absolute configuration. The major epimer of **10** (with *S* configuration on the C-6) could be separated from the mixture of four possible stereomers by careful chromatographic purification, but its configuration on C-7 carbon remained unknown.

Having in our hands the amino alcohol **10**, we preceded to further steps of the synthesis of the precursors of the carbohydrate moiety of 6-epi-VIC-105555, that is, the deoxygenation of the alcohol at terminal position C-8. For that purpose the tosylation-reduction protocol was successfully applied (Sch. 1). Reaction of amino alcohol **10** with TsCl in CH_2Cl_2 and in the presence of Et_3N resulted in formation of azetidinium salt **19**, which was isolated and its structure unambiguously confirmed by numerous data. As it can observed in Figure 3, the R_f (0.27 hexane/AcOEt/MeOH: 3/1/1) is in good agreement with the polarity of the salt **19**. The mass spectrometry gives a molecular peak at 100% at 480.2750, precise mass of the azetidinidium cation.

The NMR data of methylene protons carried by Ph are compatible with the pseudo-axial and pseudo-equatorial positions on a skeleton of azetidinium type (^{1}H NMR: $\delta = 1.37$ ppm and ^{13}C NMR: $\delta = 3.22$ ppm). They are also in good agreement with similar structures described in the literature.[20] Additionally,

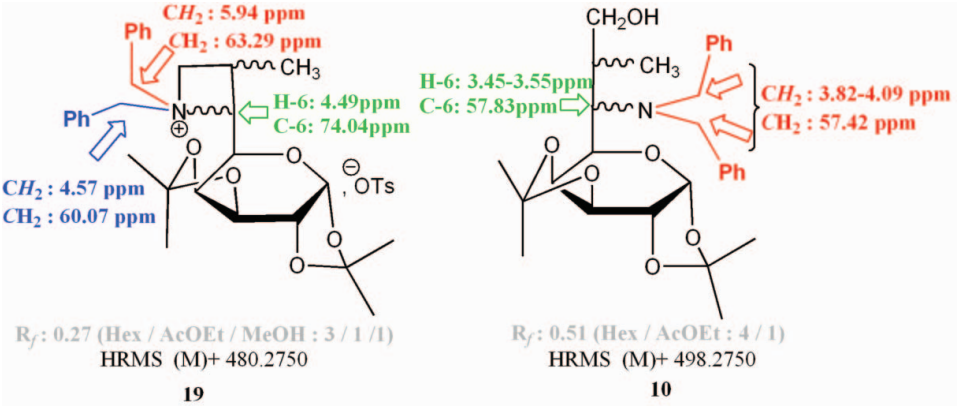


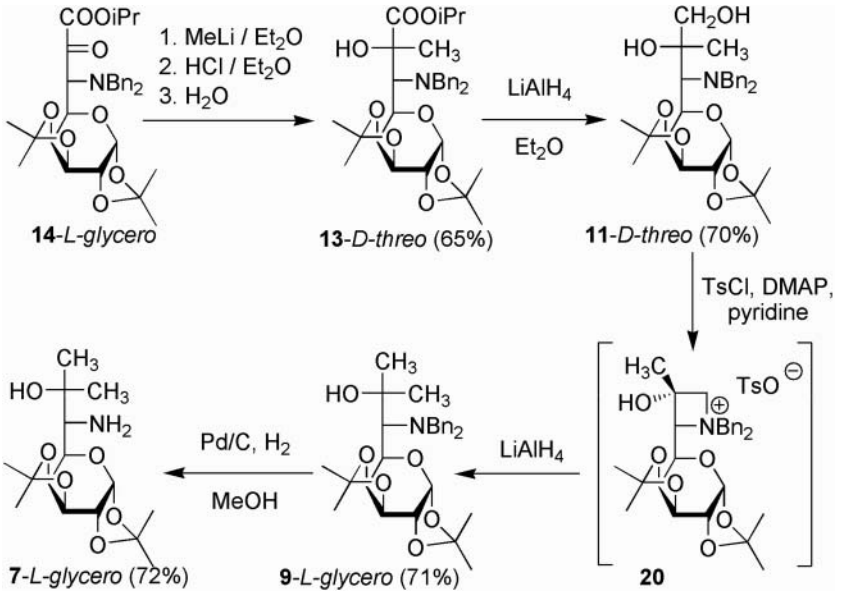
Figure 3: Characteristics of the azetidinium salt **19** (color figure available online).

the proton H-6 is more shielded in the ammonium **19** (4.49 ppm) than in the amine **10** (3.45–3.55 ppm). The chemical shifts of C-6 confirm this analysis ($\delta = 74.04$ ppm for **19** and $\delta = 57.95$ ppm for **10**). Subsequent treatment of the azetidinium salt **19** with $LiAlH_4$ afforded the desired deoxygenated derivative **8**. It has to be noted that this protocol can be performed in situ without isolation of the azetidinium salt **19**. Application of the tosylation-reduction protocol to amino alcohol **10** (the major epimer with *S* configuration on C-6 isolated by chromatography from the mixture of four possible stereomers) gave pure **8**-$_L$-*glycero*, as confirmed by X-ray analysis.[17] In turn, the use of amino alcohol **10** (mixture of $_{DL}$-*erythro*/*threo* in ratio 36/22/36/6) as substrate afforded the desired deoxygenated derivative **8** as a mixture of **8**-$_D$-*glycero*/**8**-$_L$-*glycero* in ratio 55/45, which could be enriched to 90% in **8**-$_D$-*glycero* by chromatography. Finally, in the last step of the synthesis the amino group of **8**-$_L$-*glycero* was deprotected by hydrogenation (10% Pd/C, 42 bars of H_2 during 45 h at rt) to afford, with 95% yield, the free amine **6**-$_L$-*glycero*, direct precursor of the carbohydrate fragment of 6-epi VIC-105555. It can be postulated that the hydrogenation of the **8**-$_D$-*glycero* would also afford the desired free amine with equally good yield.

Synthesis of the Carbohydrate Moiety of the C-6 Epimer of VIC-II

The success of the stereoselective preparation of the precursors of the carbohydrate fragment of 6-epi-VIC-105555 prompted us to use a similar synthetic pathway for the stereoselective preparation of the precursor of the carbohydrate fragment of another promising antibacterial, the 6-epi-VIC-II. The applied protocol is depicted in Scheme 2.

The initial reaction is methylation of the β-dibenzylamino-α-ketoester **14**-$_L$-glycero with MeLi.[21] The reaction is completely stereoselective and yields



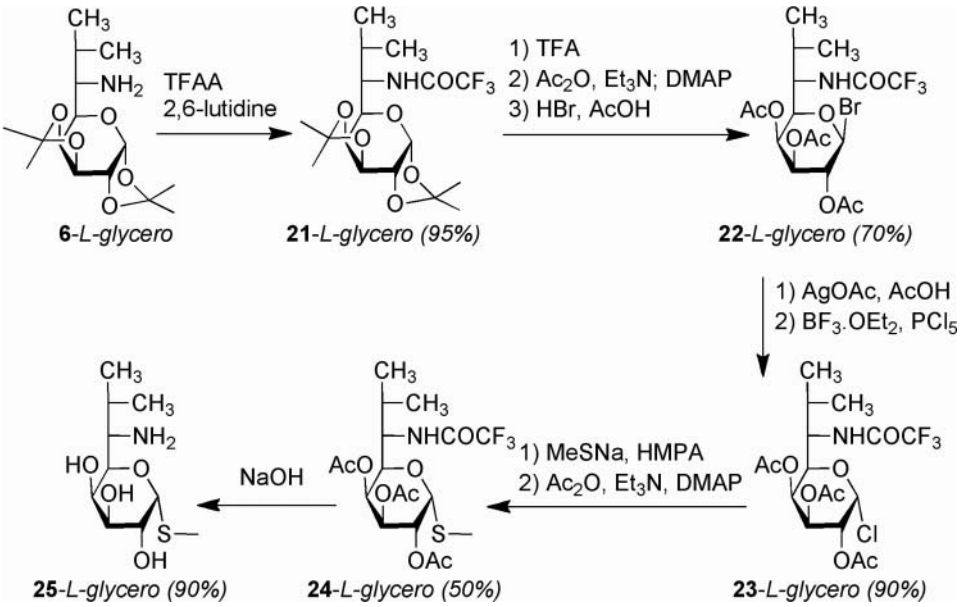
Scheme 2: Preparation of 6-epi-VIC-II.

(65%) the desired C-7 methylated tertiary alcohol **13**-$_D$-threo. This assignment was confirmed by X-ray analysis of **11**-$_D$-threo, the product of the next step, namely, the reduction of the **13**-$_D$-threo by means of $LiAlH_4$.[17] Subsequently, the deoxygenation of the alcohol at terminal position C-8 of **11**-D-threo using the, presented earlier, tosylation-reduction protocol led stereoselectively to the desired aminoalcohol **9**-$_L$-glycero (71%). In the final step, the latter was subjected for hydrogenation (10% Pd/C, 19 bars of H_2 during 32 h at rt) to afford, with 72% yield, the free amine **7**-$_L$-glycero, direct precursor of the carbohydrate fragment of 6-epi VIC-II.

Preparation of 7-Methyl-methylthio-lincosamine 25-$_L$-glycero, the Carbohydrate Core of Antibiotic 6-epi VIC 10555

To demonstrate the usefulness of our precursor of the carbohydrate moiety of new lincosamine antibiotics, we performed the complete synthesis of the carbohydrate core of the 6-epi-VIC-105555 **25**-$_L$-glycero using a literature protocol and amine **6**-$_L$-glycero as starting material (Sch. 3).[22]

First, the amine **6**-$_L$-glycero was protected in the form of trifluroacetamide **21**-$_L$-glycero. Next, total deprotection of **21**-$_L$-glycero with aqueous TFA was followed by acetylation and bromination with HBr in acetic acid to obtain **22**-$_L$-glycero. The bromide **22**-$_L$-glycero was transformed first into 1,2-tetraacetate, with the use of silver acetate (AgOAc) in acetic acid, and then into β-chloride **23**-$_L$-glycero.[22] The α-thiomethyl group installation was performed



Scheme 3: Preparation of 7-methyl-methylthio-lincosamine **25**-$_L$-*glycero,* the carbohydrate core of antibiotic 6-epi VIC 10555.

in the reaction of β-chloride **23**-$_L$-glycero with sodium thiomethoxide (MeSNa). In the final step, the complete deprotection was achieved with aqueous NaOH to obtain the desired 7-methyl-methylthio-lincosamine **25**-$_L$-glycero.

CONCLUSION

In summary, we have developed a novel route to the direct precursors of the carbohydrate moieties of new potent antibacterial agents 6-epi-VIC-105555 and 6-epi-VIC-II. While consisting of several individual synthetic steps, the presented route is featured with high-average yield per step and can be employed to synthesize a carbohydrate fragment of a variety of novel lincosamides, promising antimicrobial agents that warrant further study. In addition, in order to demonstrate the usefulness of our precursors in the synthesis of new lincosamine antibiotics we performed the complete synthesis of the carbohydrate core of the 6-epi-VIC-1055555 using our precursor as starting material.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on Bruker AC 250 MHz or Bruker Ultrashield Plus 400 MHz spectrometers. Chemical shifts (δ) are reported in

parts per million (ppm) relative to internal tetramethylsilane (Me_4Si, δ 0.0) for ^1H NMR and $CDCl_3$ (δ 77.0) for ^{13}C NMR. Coupling constants (J) are reported in hertz (Hz). Infrared spectra (IR) were recorded on a Nicolet 210 FT-IR spectrometer and were taken as thin films or as KBr discs and only the most representative frequencies (in cm^{-1}) are given. Reported melting points were measured using Electrothermal IA 9000 apparatus and are uncorrected. Optical rotations were measured on a Bellingham & Stanley limited ADP 200 polarimeter. Column chromatography was performed using silica gel 60 Merck (63–200 μm). Visualization was accomplished with UV light and exposure to EtOH/H_2SO_4 36M (80/20) solution followed by heating. Preparative TLC was performed on Merck (5535) KIESELGEL 60-F_{254} plates. All reactions were performed under an atmosphere of dry nitrogen in oven-dried glassware. All solvents for extractions and reactions were technical grade and were dried before using standard techniques. The β-dibenzylamino-α-ketoester **14**-$_L$-*glycero* and **14**-$_D$-*glycero* were synthesized using our procedure described earlier.[15]

General Procedure for the Olefination Reaction

To the solution of methyltriphenylphosphonium bromide (788 mg, 2.2 mmol) in anhydrous THF (5.0 mL) at −78°C was injected diisopropylamine (29 μL, 0.21 mmol) and nBuLi (1.3 mL of 1.6 M solution in hexane). The reaction vessel was warmed to rt during 4 h and stirred at that temperature for an additional 1 h. After that time, the reaction mixture was again cooled down to −78°C and the solution of **14-**$_L$-*glycero* (1.163 g, 2.1 mmol) in THF (3.0 mL) was added slowly. The resulting reaction mixture was warmed to rt and stirred for 14 h. After that time, the solution was hydrolyzed with H_2O (3.0 mL) and sat. aq. NaCl (2.0 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (3 × 25 mL) and dried over anh. Na_2SO_4. After filtration of drying agent the solvent was removed under vacuum, affording crude product that was further purified by column chromatography.

Isopropyl 6-*N*,*N*-Dibenzylamino-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-methylene-$_L$-*glycero*-α-$_D$-*galacto*-1,5-octopyranuronate (12-$_L$-*glycero*)

A white solid (753 mg, 65%), mp 114–115°C. R_f 0.53 (EtOAc/Hexane 1:4). $[\alpha]_D^{23}$ –53.0 (*c* 1.32, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 7.39–7.11 (H Ph, m, 10H), 6.19 (H11a, d, 1H, $J_{H11a\text{-}H11b}$ = 1.0 Hz), 5.72 (H1, d, 1H, $J_{H1\text{-}H2}$ = 5.0 Hz), 5.29 (H11b, s, 1H), 5.04 (H9, h, 1H, $J_{H9\text{-}H10}$ = 6.3 Hz), 4.61 (H5, d, 1H, $J_{H5\text{-}H6}$ = 10.9 Hz), 4.58 (H3, dd, 1H, $J_{H3\text{-}H4}$ = 7.8 Hz, $J_{H3\text{-}H2}$ = 2.5 Hz), 4.37 (H2, dd, 1H, $J_{H2\text{-}H1}$ = 5.0 Hz, $J_{H2\text{-}H3}$ = 2.5 Hz), 4.11 (H4, dd, 1H, $J_{H4\text{-}H3}$ = 7.8 Hz, $J_{H4\text{-}H5}$ = 1.8 Hz), 4.07 (H6, d, 1H, $J_{H6\text{-}H5}$ = 10.6 Hz), 3.93 (H12, d, 2H,

J = 13.6 Hz), 3.55 (H12', d, 2H, J = 13.6 Hz), 1.58 (CH_3, s, 3H), 1.37 (CH_3, s, 3H), 1.29 (CH_3, s, 3H), 1.24 (H10, d, 3H, $J_{H10\text{-}H9}$ = 6.3 Hz), 1.22 (H10', d, 3H, $J_{H10'\text{-}H9}$ = 5.6 Hz), 1.21 (CH_3, s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 167.2 (C8, 1C), 140.5 (C Ph, 2C), 137.6 (C7, 1C), 129.1, 127.7, 126.3 (CH Ph, 10C), 126.9 (C11, 1C), 109.4, 108.7 (C13, C14, 2C), 96.9 (C1, 1C), 72.1 (C4, 1C), 71.3 (C3, 1C), 70.5 (C2, 1C), 68.0 (C9, 1C), 66.8 (C5, 1C), 58.9 (C6, 1C), 54.3 (C12, C12', 2C), 26.0, 26.0, 25.2, 25.1 (CH_3*4, 4C), 21.7 (C10, C10', 2C). IR (disc, KBr) ν_{max} (cm^{-1}): 1709 (CO), 1616 (C=C), 1602, 1494 (C=C aromatic), 1455, 1382, 1372 ($C(CH_3)_2$). HRMS calcd for $C_{32}H_{42}NO_7$ $(M+H)^+$ 552.2961. Found, 552.2964.

Isopropyl 6-*N*,*N*-Dibenzylamino-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-methylene-$_D$-*glycero*-α-$_D$-*galacto*-1,5-octopyranuronate (12-$_D$-*glycero*)

Obtained as colorless oil (413 mg, 40% as a mixture of **12**-$_D$-*glycero*/**12**-$_L$-*glycero* in ratio 63:37, from which the pure major diastereoisomer was separated by column chromatography), using the general olefination protocol described above, from a mixture of **14**-$_L$-*glycero*/**14**-$_D$-*glycero* (26:74) (1.04 g, 1.89 mmol). R_f 0.53 (EtOAc/Hexane 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.39–7.10 (H Ph, m, 10H), 6.48 (H11a, d, 1H, $J_{H11a\text{-}H11b}$ = 1.1 Hz), 5.52 (H11b, s, 1H), 5.42 (H1, d, 1H, $J_{H1\text{-}H2}$ = 5.1 Hz), 5.11 (H9, h, 1H, $J_{H9\text{-}H10}$ = 6.3 Hz), 4.67 (H4, dd, 1H, $J_{H4\text{-}H3}$ = 8.0 Hz, $J_{H4\text{-}H5}$ = 1.4 Hz), 4.63–4.55 (H3, m, 1H), 4.21 (H2, dd, 1H, $J_{H2\text{-}H1}$ = 5.1 Hz, $J_{H2\text{-}H3}$ = 2.2 Hz), 4.19–4.05 (H5, H6, m, 2H), 3.84 (H12, d, 2H, J = 14.1 Hz), 3.54 (H12', d, 2H, J = 14.1 Hz), 1.39 (CH_3, s, 3H), 1.36 (CH_3, s, 3H), 1.33 (H10, d, 3H, $J_{H10\text{-}H9}$ = 6.4 Hz), 1.32 (CH_3, s, 3H), 1.32 (H10', d, 3H, $J_{H10'\text{-}H9}$ = 6.4 Hz), 1.24 (CH_3, s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 167.3 (C8, 1C), 140.4 (C Ph, 2C), 135.9 (C7, 1C), 129.0, 128.0, 126.7 (CH Ph, 10C), 128.9 (C11, 1C), 108.7, 108.2 (C13, C14, 2C), 96.7 (C1, 1C), 71.0, 71.0 (C3, C4, 2C), 70.8 (C2, 1C), 68.1 (C9, 1C), 66.1, 60.4 (C5, C6, 2C), 56.2 (C12, C12', 2C), 25.9, 25.8, 24.8, 24.4 (CH_3*4, 4C), 21.9, 21.9 (C10, C10', 2C). IR (disc, KBr) ν_{max} (cm^{-1}): 1709 (CO), 1616 (C=C), 1602, 1602 (C=C aromatic), 1455, 1382, 1372 ($C(CH_3)_2$).

General Procedure for Reduction of the Olefine 12-$_D$-*Glycero*/12-$_L$-*glycero* by Means of $LiAlH_4$

To the solution of two epimers **12**-$_L$-*glycero*/**12**-$_D$-*glycero* (157.0 mg, 0.27 mmol, in ratio 46/54) in Et_2O (4.0 mL) at −78°C was added slowly $LiAlH_4$ (0.45 mL of 1M solution in Et_2O) and an additional portion of Et_2O (5.0 mL). The resulting reaction mixture was stirred at −78°C for 8 h and then at rt for an additional 15 h. After that time, the solution was hydrolyzed with 5% sol. aq. NaOH (0.15 mL). Next, the solution was centrifuged three times and washed with Et_2O (2 × 15 mL). The combined organic extracts were dried over anh. Na_2SO_4 and after filtration of drying agent the solvent was removed

under vacuum, affording crude product that was further purified by column chromatography. The purified compound **10** (130 mg, 92%) was a mixture of four possible diastereoisomers: **10**-$_D$-*threo* + **10**-$_L$-*erythro* (in ratio 44/2) and **10**-$_D$-*erythro* + **10**-$_L$-*threo* (in ratio 40/14).

6-*N*,*N*-Dibenzylamino-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-*C*-methyl-$_D$-*threo* and $_L$-*erythro*-α-$_D$-*galacto*-1,5-octopyranitol (10-$_D$-*threo* and 10-$_L$-*erythro*)

Major epimer. Colorless oil. $[\alpha]_D^{23}$ −70.5 (*c* 1.0, CH_2Cl_2). R_f 0.25 (EtOAc/Hexane 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.48–7.17 (H Ph, m, 10H), 5.71 (H1, d, 1H, $J_{H1\text{-}H2} = 5.3$ Hz), 4.63 (H3, dd, 1H, $J_{H3\text{-}H4} = 7.8$ Hz, $J_{H3\text{-}H2} = 2.3$ Hz), 4.44 (H5, d, 1H, $J_{H5\text{-}H6} = 9.8$ Hz), 4.36 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.3$ Hz, $J_{H2\text{-}H3} = 2.5$ Hz), 4.33 (H4, dd, 1H, $J_{H4\text{-}H3} = 9.6$, $J_{H4\text{-}H5} = 1.3$ Hz), 4.02 (H10, d, 2H, $J = 13.4$ Hz), 3.93–3.78 (H10', m, 2H), 3.60–3.47 (H8, m, 2H), 3.18–3.08 (H6, m, 1H), 1.96–1.82 (H7, m, 1H), 1.60 (CH_3, s, 3H), 1.53 (CH_3, s, 3H), 1.39 (CH_3, s, 3H), 1.32 (CH_3, s, 3H), 0.64 (H9, d, 3H, $J_{H9\text{-}H7} = 6.8$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C δ 140.8 (C Ph, 2C), 129.8, 128.0, 126.7 (CH Ph, 10C), 109.1, 108.6 (C11, C12, 2C), 96.8 (C1, 1C), 72.4 (C4, 1C), 71.3 (C3, 1C), 70.3, 70.0 (C2, C5, 2C), 65.7 (C8, 1C), 58.4 (C6, 1C), 56.3 (C10, C10', 2C), 36.0 (C7, 1C), 26.2, 25.9, 25.1, 24.7 (CH_3*4, 4C), 16.2 (C9, 1C). IR (film, CCl_4) ν_{max} (cm^{-1}): 3600–3200 (OH), 1602, 1494 (C=C aromatic), 1454, 1380, 1371 ($C(CH_3)_2$). HRMS calcd for $C_{29}H_{40}NO_6$ $(M+H)^+$ 498.2856. Found, 498.2858.

Minor epimer. Colorless oil. $[\alpha]_D^{23}$ –58.7 (*c* 1.5, CH_2Cl_2). R_f 0.18 (EtOAc/Hexane 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.60–7.15 (H Ph, m, 10H), 5.75 (H1, d, 1H, $J_{H1\text{-}H2} = 5.3$ Hz), 4.66 (H3, dd, 1H, $J_{H3\text{-}H4} = 8.1$ Hz, $J_{H3\text{-}H2} = 2.5$ Hz), 4.41 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.3$ Hz, $J_{H2\text{-}H3} = 2.5$ Hz), 4.34 (H5, dd, 1H, $J_{H5\text{-}H6} = 10.4$ Hz, $J_{H5\text{-}H4} = 1.8$ Hz), 4.17 (H4, dd, 1H, $J_{H4\text{-}H3} = 8.1$, $J_{H4\text{-}H5} = 1.8$ Hz), 4.09–3.82 (H10, H10', m, 4H), 3.55–3.45 (H6, m, 1H), 3.45–3.35 (H8, m, 1H), 3.13 (H8', dd, 1H, $J_{H8'\text{-}H8} = 10.9$ Hz, $J_{H8'\text{-}H7} = 2.3$ Hz), 1.77–1.67 (H7, m, 1H), 1.59 (CH_3, s, 3H), 1.52 (CH_3, s, 3H), 1.40 (CH_3, s, 3H), 1.31 (CH_3, s, 3H), 1.18 (H9, d, 3H, $J_{H9\text{-}H7} = 7.1$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 129.4–126.7 (CH Ph, 10C), 109.4, 108.8 (C11, C12, 2C), 96.7 (C1, 1C), 71.5 (C4, 1C), 71.0 (C3, 1C), 70.2 (C2, 1C), 68.5 (C5, 1C), 67.4 (C8, 1C), 57.8 (C6, 1C), 57.4 (C10, C10', 2C), 34.2 (C7, 1C), 26.2, 25.9, 25.0, 24.6 (CH_3*4, 4C), 12.5 (C9, 1C).

6-*N*,*N*-Dibenzylamino-6,7-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-*C*-methyl-$_D$-*erythro* and $_L$-*threo*-α-$_D$-*galacto*-1,5-octopyranitol (10-$_D$-*erythro* and 10-$_L$-*threo*)

Major epimer. Colorless oil. R_f 0.19 (EtOAc/Hexane 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.41–7.24 (Ph, m, 10H), 5.49 (H1, d, 1H, $J_{H1\text{-}H2} = 5.1$ Hz), 4.60–4.53 (H3, H4, m, 2H), 4.26 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.1$ Hz, $J_{H2\text{-}H3} = 1.7$ Hz), 4.09 (H5, d, 1H, $J_{H5\text{-}H6} = 9.9$ Hz), 3.78 (H10, d, 2H, $J = 13.5$ Hz),

3.62–3.52 (H10', H8, m, 4H), 3.12 (H6, dd, 1H, $J_{H6\text{-}H5} = 9.9$ Hz, $J_{H6\text{-}H7} = 1.2$ Hz), 2.39–2.28 (H7, m, 1H), 1.50 (CH_3, s, 3H), 1.34 (CH_3, s, 3H), 1.30 (CH_3, s, 3H), 1.24 (CH_3, s, 3H), 1.07 (H9, d, 3H, $J_{H9\text{-}H7} = 7.1$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 139.5 (C Ph, 2C), 129.5, 128.0, 126.9 (CH Ph, 10C), 108.6, 108.5 (C11, C12, 2C), 96.7 (C1, 1C), 71.4 (C4, 1C), 70.9, 70.9 (C3, C2, 2C), 68.3 (C8, 1C), 65.9 (C5, 1C), 57.9 (C6, 1C), 55.1 (C10, C10', 2C), 32.9 (C7, 1C), 25.9, 25.8, 24.8, 24.3 (CH_3*4, 4C), 13.8 (C9, 1C).

Minor epimer. Colorless oil. R_f 0.18 (EtOAc/Hexane 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.41–7.24 (Ph, m, 10H), 5.55 (H1, d, 1H, $J_{H1\text{-}H2} = 5.2$ Hz), 4.70 (H3, dd, 1H, $J_{H3\text{-}H4} = 8.0$ Hz, $J_{H3\text{-}H2} = 2.1$ Hz), 4.44 (H4, dd, 1H, $J_{H4\text{-}H3} = 8.0$ Hz, $J_{H4\text{-}H5} = 1.3$ Hz), 4.32 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.2$ Hz, $J_{H2\text{-}H3} = 2.1$ Hz), 4.13 (H5, d, 1H, $J_{H5\text{-}H6} = 9.9$ Hz), 3.82 (H10, d, 2H, $J = 14.2$ Hz), 3.68 (H10', d, 2H, $J = 13.1$ Hz), 3.44 (H8, dd, 1H, $J_{H8\text{-}H8'} = 11.1$ Hz, $J_{H8\text{-}H7} = 6.4$ Hz), 3.33 (H8', dd, 1H, $J_{H8'\text{-}H8} = 11.1$ Hz, $J_{H8'\text{-}H7} = 4.0$ Hz), 3.25 (H6, dd, 1H, $J_{H6\text{-}H5} = 9.1$ Hz, $J_{H6\text{-}H7} = 4.1$ Hz), 2.15–2.05 (H7, m, 1H), 1.56 (CH_3, s, 3H), 1.44 (CH_3, s, 3H), 1.32 (CH_3, s, 3H), 1.26 (CH_3, s, 3H), 1.08 (H9, d, 3H, $J_{H9\text{-}H7} = 7.3$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 139.8 (C Ph, 2C), 128.8, 128.3, 127.3 (CH Ph, 10C), 109.0, 108.4 (C11, C12, 2C), 96.8 (C1, 1C), 72.6 (C4, 1C), 71.2 (C3, 1C), 70.6 (C2, 1C), 66.5 (C8, 1C), 65.3 (C5, 1C), 56.7 (C6, 1C), 55.7 (C10, C10', 2C), 35.5 (C7, 1C), 26.1, 26.0, 24.8, 24.5 (CH_3*4, 4C), 13.3 (C9, 1C).

Preparation of the Azetidinium Salt 19

To the solution of pure major epimer (117.0 mg, 0.36 mmol, from mixture **10-**$_D$*-threo* and **10-**$_L$*-erythro*) in CH_2Cl_2 (6.0 mL) at rt was added neat Et_3N (0.15 mL, 1.07 mmol) and DMAP (43.0 mg, 0.36 mmol). The resulting reaction mixture was cooled down to 0°C and TsCl (136.0 mg, 0.71 mmol) was added. After completion of the addition, the reaction mixture was warmed to rt and stirred for 18 h. After that time, the solution was hydrolyzed with sat. aq. sol. of $NaHCO_3$ (2.0 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anh. Na_2SO_4 and after filtration of drying agent the solvent was removed under vacuum, affording crude product that was further purified by column chromatography, affording the desired product **19** (54.0 mg, 23%) as a pale yellow oil. R_f 0.27 (EtOAc/Hexane/MeOH 1:3:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.87–7.07 (H Ph, m, 14H), 5.94 (H10a, d, 1H, $J_{H10a\text{-}H10b} = 12.5$ Hz), 5.66 (H1, d, 1H, $J_{H1\text{-}H2} = 5.1$ Hz), 4.78 (H5, dd, 1H, $J_{H5\text{-}H6} = 10.2$ Hz, $J_{H5\text{-}H4} = 1.5$ Hz), 4.70 (H3, dd, 1H, $J_{H3\text{-}H4} = 8.0$ Hz, $J_{H3\text{-}H2} = 2.5$ Hz), 4.69–4.63 (H8, m, 1H), 4.57 (H10b, d, 1H, $J_{H10b\text{-}H10a} = 12.3$ Hz), 4.53–4.45 (H6, m, 1H), 4.42 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.1$ Hz, $J_{H2\text{-}H3} = 2.5$ Hz), 4.21 (H4, dd, 1H, $J_{H4\text{-}H3} = 8.0$ Hz, $J_{H4\text{-}H5} = 1.7$ Hz), 4.11 (H10'a, d, 1H, $J_{H10'a\text{-}H10'b} = 14.0$ Hz), 4.12–4.02 (H7, m, 1H), 3.85 (H10'b, d, 1H, $J_{H10'b\text{-}H10'a} = 12.8$ Hz), 3.38–3.31 (H8', m, 1H), 2.31 (CH_3 TsO-, s, 3H), 1.60 (CH_3, s, 3H), 1.49 (CH_3, s, 3H), 1.34 (CH_3, s, 3H), 1.27 (CH_3, s,

3H), 0.73 (H9, d, 3H, $J_{H9\text{-}H7} = 6.4$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 144.2, 138.7, 128.0, 127.8 (C Ph, 4C), 133.7, 133.5, 130.9, 130.5, 129.5, 129.3, 128.3, 126.2 (CH Ph, 14C), 109.9, 109.5 (C11, C12, 2C), 96.2 (C1, 1C), 74.0 (C6, 1C), 70.6 (C3, 1C), 70.1 (C2, 1C), 69.1 (C4, 1C), 65.1 (C5, 1C), 60.1 (C10, 1C), 63.3 (C10', 1C), 59.5 (C8, 1C), 50.6 (C7, 1C), 26.0, 25.7, 24.8, 24.0 (CH_3*4, 4C), 21.3 (CH_3 TsO-, 1C), 16.3 (C9, 1C). IR (film, CCl_4) ν_{max} (cm^{-1}): 1600, 1497 (C=C aromatic), 1456, 1381 ($C(CH_3)_2$). HRMS calcd for $C_{29}H_{38}NO_5$ $(M)^+$ 480.2750. Found, 480.2750.

Preparation of 6-*N*,*N*-Dibenzylamino-1,2:3,4-di-*O*-isopropylidene-7-*C*-methyl-6,7,8-trideoxy-$_L$-*glycero*-α-$_D$-*galacto*-1,5-octopyranose (8-$_L$-*glycero*)

To the solution of azetidinium salt **19** (52.0 mg, 0.080 mmol) in Et_2O/THF (2.0 mL/3.0 mL) mixture, $LiAlH_4$ (0.2 mL of 1M sol. in Et_2O) was added at rt and the resulting solution was stirred at that temperature for 2 h. After that time, the reaction mixture was hydrolyzed with 5% sol. aq. NaOH (0.10 mL), centrifuged three times, and washed with Et_2O (2 × 10 mL). The combined organic layers were dried over anh. Na_2SO_4 and after filtration of drying agent the solvent was removed under vacuum, affording crude product that was further purified by column chromatography, affording the desired product **8**-$_L$-*glycero*. White solid (38.0 mg, 99%) mp 132–133°C. $[\alpha]_D^{23}$ –81.6 (*c* 0.76, CH_2Cl_2). R_f 0.58 (EtOAc/Hexane 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.90–7.35 (H Ph, m, 10H), 5.72 (H1, d, 1H, $J_{H1\text{-}H2} = 5.2$ Hz), 4.63 (H3, dd, 1H, $J_{H3\text{-}H4} = 7.9$ Hz, $J_{H3\text{-}H2} = 2.5$ Hz), 4.38 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.2$ Hz, $J_{H2\text{-}H3} = 2.5$ Hz), 4.26 (H5, dd, 1H, $J_{H5\text{-}H6} = 10.3$ Hz, $J_{H5\text{-}H4} = 1.6$ Hz), 4.19 (H4, dd, 1H, $J_{H4\text{-}H3} = 7.9$ Hz, $J_{H4\text{-}H5} = 1.7$ Hz), 3.96 (H9, d, 2H, $J = 13.3$ Hz), 3.83 (H9', d, 2H, $J = 12.6$ Hz), 3.04 (H6, dd, 1H, $J_{H6\text{-}H5} = 10.3$ Hz, $J_{H6\text{-}H7} = 3.1$ Hz), 1.77–1.68 (H7, m, 1H), 1.60 (CH_3, s, 3H), 1.52 (CH_3, s, 3H), 1.40 (CH_3, s, 3H), 1.32 (CH_3, s, 3H), 0.89 (H8, d, 3H, $J_{H8\text{-}H7} = 7.2$ Hz), 0.64 (H8', d, 3H, $J_{H8'\text{-}H7} = 6.7$ Hz).^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 141.5 (C Ph, 2C), 129.8, 127.9, 126.5 (CH Ph, 10C), 109.2, 108.6 (C10, C11, 2C), 96.9 (C1, 1C), 72.3 (C4, 1C), 71.2 (C3, 1C), 70.4 (C2, 1C), 69.8 (C5, 1C), 58.3 (C6, 1C), 57.2 (C9, C9', 2C), 28.8 (C7, 1C), 26.3, 26.0, 25.1, 24.9 (CH_3*4, 4C), 21.6 (C8', 1C), 17.5 (C8, 1C). IR (film, CCl_4) ν_{max} (cm^{-1}): 1600, 1494 (C=C aromatic), 1453, 1382, 1370 ($C(CH_3)_2$). HRMS calcd for $C_{29}H_{39}NO_5$ $(M)^+$ 481.2828. Found, 481.2828.

Preparation of 6-*N*,*N*-Dibenzylamino-1,2:3,4-di-*O*-isopropylidene-7-*C*-methyl-6,7,8-trideoxy-$_D$-glycero-α-$_D$-galacto-1,5-octopyranose (8-$_D$-*glycero*)

Prepared from the mixture of four possible diastereoisomers of amino alcohol **10** (38.0 mg, 0.076 mmol; composition of the mixture was **10**-$_D$-*threo* +

10-$_L$-*erythro* and **10**-$_D$-*erythro* + **10**-$_L$-*threo* in ratio 36/6/36/22). The overall yield, after two steps, of the purified product (a mixture of **8**-$_L$-*glycero*/**8**-$_D$-*glycero* in ratio 45/55) was 75% (28.0 mg). The sample of **8**-$_D$-*glycero* (enriched to 90% in the desired epimer) was obtained after the second chromatographic purification as colorless oil. $[\alpha]_D^{23}$ –18.5 (c 0.65, CH_2Cl_2). R_f 0.56 (EtOAc/Hexane 1:8). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.47–7.19 (H Ph, m, 10H), 5.51 (H1, d, 1H, $J_{H1\text{-}H2} = 5.1$ Hz), 4.61 (H3, dd, 1H, $J_{H3\text{-}H4} = 8.0$ Hz, $J_{H3\text{-}H2} = 2.1$ Hz), 4.51 (H4, dd, 1H, $J_{H4\text{-}H3} = 8.0$ Hz, $J_{H4\text{-}H5} = 1.4$ Hz), 4.26 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.1$ Hz, $J_{H2\text{-}H3} = 2.1$ Hz), 4.05 (H5, dd, 1H, $J_{H5\text{-}H6} = 10.0$ Hz, $J_{H5\text{-}H4} = 1.1$ Hz), 3.77 (H9, d, 2H, $J = 13.4$ Hz), 3.65 (H9', d, 2H, $J = 13.4$ Hz), 2.95 (H6, dd, 1H, $J_{H6\text{-}H5} = 10.0$ Hz, $J_{H6\text{-}H7} = 2.1$ Hz), 2.23–2.13 (H7, m, 1H), 1.51 (CH_3, s, 3H), 1.38 (CH_3, s, 3H), 1.34 (CH_3, s, 3H), 1.32 (CH_3, s, 3H), 0.99 (H8, d, 3H, $J_{H8\text{-}H7} = 7.2$ Hz), 0.94 (H8', d, 3H, $J_{H8'\text{-}H7} = 6.9$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 140.2 (C Ph, 2C), 129.4, 128.0, 126.8 (CH Ph, 10C), 108.6, 108.2 (C10, C11, 2C), 96.8 (C1, 1C), 71.8 (C4, 1C), 71.1 (C3, 1C), 70.7 (C2, 1C), 66.5 (C5, 1C), 59.2 (C6, 1C), 55.6 (C9, C9', 2C), 26.3 (C7, 1C), 26.0, 25.9, 24.9, 24.5 (CH_3*4, 4C), 21.2 (C8, 1C), 19.8 (C8', 1C).

Preparation of 6-Amino-1,2:3,4-di-*O*-isopropylidene-7-*C*-methyl-6,7,8-trideoxy-$_L$-*glycero*-α-$_D$-*galacto*-1,5-octopyranose (6-$_L$-*glycero*), the Direct Precursor of the Carbohydrate Moiety of 6-epi VIC-105555

To the solution of compound **8**-$_L$-*glycero* (27.0 mg, 0.056 mmol) in MeOH (10.0 mL) was added 10% Pd/C (10.0 mg) and the resulting solution was stirred under atmosphere of H_2 (19 bars) for 45 h. After completion of the reaction, the resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure, affording desired product, the primary amine **6**-*L-glycero* (16.0 mg, 95%), that does not require any further purification. Colorless oil. $[\alpha]_D^{23}$ –47.0 (*c* 1.15, CH_2Cl_2). R_f 0.28 (EtOAc/Hexane/MeOH 1:3:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.59 (H1, d, 1H, $J_{H1\text{-}H2} = 5.1$ Hz), 4.58 (H3, dd, 1H, $J_{H3\text{-}H4} = 8.0$ Hz, $J_{H3\text{-}H2} = 2.3$ Hz), 4.30 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.1$ Hz, $J_{H2\text{-}H3} = 2.3$ Hz), 4.25 (H4, dd, 1H, $J_{H4\text{-}H3} = 8.0$ Hz, $J_{H4\text{-}H5} = 1.7$ Hz), 3.57 (H5, dd, 1H, $J_{H5\text{-}H6} = 7.0$ Hz, $J_{H5\text{-}H4} = 1.6$ Hz), 2.89 (H6, dd, 1H, $J_{H6\text{-}H5} = 7.0$ Hz, $J_{H6\text{-}H7} = 3.5$ Hz), 1.99–1.90 (H7, m, 1H), 1.53 (CH_3, s, 3H), 1.46 (CH_3, s, 3H), 1.33 (CH_3*2, s, 6H), 1.02 (H8, d, 3H, $J_{H8\text{-}H7} = 6.8$ Hz), 0.90 (H8', d, 3H, $J_{H8'\text{-}H7} = 6.8$ Hz).^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 109.2, 108.5 (C9, C10, 2C), 96.8 (C1, 1C), 72.0 (C4, 1C), 71.0 (C3, 1C), 70.6 (C2, 1C), 69.4 (C5, 1C), 55.6 (C6, 1C), 29.0 (C7, 1C), 26.1, 26.0, 25.0, 24.3 (CH_3*4, 4C), 20.5 (C8, 1C), 15.9 (C8', 1C). IR (film, CCl_4) ν_{max} (cm^{-1}): 3390 (NH_2), 1459, 1381 ($C(CH_3)_2$). HRMS calcd for $C_{15}H_{28}NO_5$ $(M+H)^+$ 302.1967. Found, 302.1968.

Preparation of Isopropyl 6-Deoxy-6-N,N-dibenzylamino-1,2:3,4-di-*O*-isopropylidene-7-*C*-methyl-$_D$-*threo*-α-$_D$-*galacto*-1, 5-octopyranuronate (13-$_D$-*threo*)

To the solution of **14**-$_L$-*glycero* (823 g, 1.49 mmol) in Et_2O (7.0 mL) at −78°C was gradually injected MeLi (1.0 mL of 1.6 M sol in Et_2O). After the addition was completed, the resulting reaction mixture was stirred at −78°C for 0.75 h and then warmed to 0°C and stirred at that temperature for an additional 0.5 h. After that time, the reaction mixture was cooled down to −35°C and was hydrolyzed with sat. Et_2O solution of HCl (3.0 mL) and H_2O (3.0 mL). The layers were separated and the aqueous layer was extracted with Et_2O (3 × 20 mL) and CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over anh. Na_2SO_4. After filtration of drying agent the solvent was removed under vacuum, affording crude product that was further purified by column chromatography to give **13**-$_D$-*threo*. Colorless oil (550 mg, 65%). $[\alpha]_D^{23}$ –99.3 (*c* 0.73, CH_2Cl_2). R_f 0.45 (EtOAc/Hexane 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.57–7.05 (H Ph, m, 10H), 5.68 (H1, d, 1H, $J_{H1\text{-}H2} = 5.1$ Hz), 4.75 (H9, h, 1H, $J_{H9\text{-}H10} = 6.3$ Hz), 4.59 (H3, dd, 1H, $J_{H3\text{-}H4} = 8.0$ Hz, $J_{H3\text{-}H2} = 2.4$ Hz), 4.37–4.32 (H2, H5, m, 2H), 4.26 (H4, dd, 1H, $J_{H4\text{-}H3} = 8.0$ Hz, $J_{H4\text{-}H5} = 1.4$ Hz), 4.20–3.70 (H12, H12', m, 4H), 3.59 (H6, d, 1H, $J_{H6\text{-}H5} = 10.4$ Hz), 1.57, 1.49, 1.42, 1.38, 1.27 (H11, CH_3*4, 5s, 15H), 1.06 (H10, d, 3H, $J_{H10\text{-}H9} = 6.2$ Hz), 0.95 (H10', d, 3H, $J_{H10'\text{-}H9} = 6.3$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 175.7 (C8, 1C), 130.7–127.0 (CH Ph, 10C), 109.1, 108.8 (C13, C14, 2C), 96.7 (C1, 1C), 73.5 (C7, 1C), 71.5 (C4, 1C), 71.0 (C3, 1C), 70.3 (C2, 1C), 68.8 (C9, 1C), 68.2 (C5, 1C), 59.8 (C6, 1C), 58.2, 54.7 (C12, C12', 2C), 26.2, 26.0, 25.0, 24.4, 23.5 (C11, CH_3*4, 5C), 21.5, 21.4 (C10, C10', 2C). IR (film, CCl_4) ν_{max} (cm^{-1}): 3600–3300 (OH), 1720 (CO), 1602, 1495 (C=C), 1453, 1380, 1372 ($C(CH_3)_2$). HRMS calcd for $C_{32}H_{44}NO_8$ $(M+H)^+$ 570.3067. Found, 570.3070.

Preparation of 6-Deoxy-6-*N*,*N*-dibenzylamino-1,2:3,4-di-*O*-isopropylidene-7-*C*-methyl-$_D$-*threo*-α-$_D$-*galacto*-1, 5-octopyranitol (11-$_D$-*threo*)

The solution of hydroxy ester **13**-$_D$-*threo* (305 mg, 0.54 mmol) in Et_2O (4.0 mL) was added at 0°C to the solution of $LiAlH_4$ (1.1 mL of 1M sol. in Et_2O). The resulting reaction mixture was stirred at rt for 52 h. After that time, the reaction mixture was hydrolyzed with 5% sol. aq. NaOH (0.3 mL), centrifuged three times, and washed with Et_2O (2 × 10 mL). The combined organic layers were dried over anh. Na_2SO_4 and after filtration of drying agent the solvent was removed under vacuum, affording crude product that was further purified by column chromatography, affording **11**-$_D$-*threo*. White solid (192.0 mg, 70%) mp 138–139°C. $[\alpha]_D^{23}$ –109.3 (*c* 0.75, CH_2Cl_2). R_f 0.38 (EtOAc/Hexane 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.54–7.01 (H Ph, m, 10H), 5.73 (H1, d, 1H, $J_{H1\text{-}H2} =$

5.1 Hz), 4.66 (H3, dd, 1H, $J_{H3\text{-}H4} = 7.9$ Hz, $J_{H3\text{-}H2} = 2.5$ Hz), 4.39 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.1$ Hz, $J_{H2\text{-}H3} = 2.5$ Hz), 4.32 (H5, d, 1H, $J_{H5\text{-}H6} = 10.3$ Hz), 4.17 (H4, dd, 1H, $J_{H4\text{-}H3} = 8.0$ Hz, $J_{H4\text{-}H5} = 1.3$ Hz), 4.20–4.07 (H8, m, 2H), 3.95 (H10a, d, 1H, $J_{H10a\text{-}H10b} = 12.4$ Hz), 3.75 (H10b, d, 1H, $J_{H10b\text{-}H10a} = 12.2$ Hz), 3.43 (H6, d, 1H, $J_{H6\text{-}H5} = 10.3$ Hz), 3.23 (H10'a, d, 1H, $J_{H10'a\text{-}H10'b} = 11.3$ Hz), 3.17 (H10'b, d, 1H, $J_{H10'b\text{-}H10'a} = 11.3$ Hz), 1.56, 1.39, 1.33, 1.19 (H9, CH_3*4, 4s, 15H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 139.8, 138.7 (C Ph, 2C), 130.9, 130.4, 129.5, 128.7, 128.2, 127.3 (CH Ph, 10C), 109.5, 108.8 (C11, C12, 2C), 96.7 (C1, 1C), 72.2 (C4, 1C), 71.2 (C3, 1C), 70.2 (C2, 1C), 70.1 (C7, 1C), 69.6 (C10, 1C), 68.3 (C5, 1C), 57.6 (C10', 1C), 57.6 (C6, 1C), 54.8 (C8, 1C), 26.1, 26.0, 25.0, 24.3, 22.9 (C9, CH_3*4, 5C). IR (disc, KBr) ν_{max} (cm^{-1}): 3600–3300 (OH), 1602, 1494 (C=C), 1452, 1380 ($C(CH_3)_2$). HRMS calcd for $C_{29}H_{40}NO_7$ $(M+H)^+$ 514.2805. Found, 514.2807.

Synthesis of 6-*N*,*N*-Dibenzylamino-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-*C*-methyl-L-*glycero*-α-D-*galacto*-1,5-octopyranose (9-L-*glycero*)

The synthesis was done in one pot, using the protocol described earlier. The corresponding azetidinium salt **20** was not isolated but directly reduced by means of $LiAlH_4$ (5.0 equiv.) to furnish the desired **9**-L-*glycero*. Starting from **11**-D-*threo* (157.0 mg, 0.31 mmol), the overall yield, after two steps, of the purified product was 71% (108.0 mg). Colorless oil. $[\alpha]_D^{23}$ –106.7 (c 0.9, CH_2Cl_2). R_f 0.36 (EtOAc/Hexane 1:4). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 7.53–7.05 (H Ph, m, 10H), 5.72 (H1, d, 1H, $J_{H1\text{-}H2} = 5.1$ Hz), 4.64 (H3, dd, 1H, $J_{H3\text{-}H4} = 7.8$ Hz, $J_{H3\text{-}H2} = 2.3$ Hz), 4.37 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.1$ Hz, $J_{H2\text{-}H3} = 2.4$ Hz), 4.32–4.24 (H4, H5, m, 2H), 4.19–4.08 (H9, m, 2H), 3.94 (H9'a, d, 1H, $J_{H9'a\text{-}H9'b} = 12.0$ Hz), 3.71 (H9'b, d, 1H, $J_{H9'b\text{-}H9'a} = 11.8$ Hz), 3.17 (H6, d, 1H, $J_{H6\text{-}H5} = 10.2$ Hz), 1.56, 1.55, 1.39, 1.32, 1.19, 1.07 (C8, C8', CH_3*4, 6s, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 140.6, 139.3 (C Ph, 2C), 130.5, 129.1, 128.5, 128.0, 127.0 (CH Ph, 10C), 109.1, 108.7 (C10, C11, 2C), 96.8 (C1, 1C), 72.5 (C4, 1C), 71.1 (C3, 1C), 70.3 (C2, 1C), 69.0 (C7, 1C), 68.6 (C5, 1C), 62.9 (C6, 1C), 58.4, 54.8 (C9, C9', 2C), 29.7, 28.2, 26.2, 26.0, 25.0, 24.4 (C8, C8', CH_3*4, 6C). IR (film, CCl_4) ν_{max} (cm^{-1}): 3600–3200 (OH), 1487 (C=C), 1456, 1384, 1370 ($C(CH_3)_2$). HRMS calcd for $C_{29}H_{40}NO_6$ $(M+H)^+$ 498.2856. Found, 498.2856.

Preparation of 6-Amino-6,8-dideoxy-1,2:3,4-di-*O*-isopropylidene-7-*C*-methyl-L-*glycero*-α-D-*galacto*-1,5-octopyranose (7-L-*glycero*), the Direct Precursor of the Carbohydrate Moiety of 6-epi-VIC-II

To the solution of compound **9**-L-*glycero* (46.0 mg, 0.092 mmol) in MeOH (6.0 mL) was added 10% Pd/C (23.0 mg) and the resulting solution was stirred

under atmosphere of H_2 (19 bars) for 32 h. After completion of the reaction, the resulting mixture was filtered through a pad of Celite and the filtrate was concentrated under reduced pressure, affording the desired product, the primary amine **7**-L-*glycero* (21.0 mg, 72%) that does not require any further purification. Colorless oil. $[\alpha]_D^{23}$ –60.8 (c 1.25, CH_2Cl_2). R_f 0.24 (EtOAc/Hexane/MeOH 1:3:1). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.58 (H1, d, 1H, $J_{H1\text{-}H2} = 5.1$ Hz), 4.58 (H3, dd, 1H, $J_{H3\text{-}H4} = 7.9$ Hz, $J_{H3\text{-}H2} = 2.3$ Hz), 4.31 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.1$ Hz, $J_{H2\text{-}H3} = 2.3$ Hz), 4.23 (H4, dd, 1H, $J_{H4\text{-}H3} = 7.9$ Hz, $J_{H4\text{-}H5} = 1.9$ Hz), 3.86–3.76 (H5, m, 1H), 2.84–2.74 (H6, m, 1H), 1.53, 1.46, 1.33, 1.23, 1.13 (H8, H8', CH_3*4, 5s, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ_C 109.2, 108.5 (C9, C10, 2C), 96.7 (C1, 1C), 75.1 (C4, 1C), 71.3 (C7, 1C), 71.0 (C3, 1C), 70.4 (C2, 1C), 63.9 (C5, 1C), 60.5 (C6, 1C), 26.6, 26.0, 26.0, 24.8, 24.2 (C8, C8', CH_3*4, 6C). IR (film, CCl_4) ν_{max} (cm^{-1}): 3600–3100 (OH), 1653 (NH), 1456, 1386, 1373 ($C(CH_3)_2$). HRMS calcd for $C_{15}H_{28}NO_6$ $(M+H)^+$ 318.1917. Found, 318.1920.

Synthesis of 6-Trifluoroacetylamino-7-*C*-methyl-6,7,8-trideoxy-1,2:3,4-di-*O*-isopropylidene-L-*glycero*-α-D-*galacto*-1,5-octopyranose (21-L-*glycero*)

To a solution of amine **6**-L-*glycero* (800 mg, 1.32 mmol) and 2,6-lutidine (0.62 mL, 5.31 mmol) in dry CH_2Cl_2 (30 mL) at 0°C was added trifluoroacetic anhydride (TFAA) (0.28 mL, 1.98 mmol). The resulting reaction mixture was stirred at 0°C for 15 min and then at rt for 3 h. After that time, the reaction was quenched with H_2O (100 mL) and extracted with EtOAc (3 × 20 mL). The layers were separated and the organic phase was washed with 1.0 N HCl (2 × 20 mL), sat. aq. $NaHCO_3$ (2 × 20 mL), and brine (2 × 20 mL). The combined organic extracts were dried over anh. Na_2SO_4 and concentrated to give crude **21**-L-glycero (colorless oil, 95%, 997 mg) that was used without purification in the next step. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.60 (H1, d, 1H, $J_{H1\text{-}H2} = 5.0$ Hz), 4.64 (H3, dd, 1H, $J_{H3\text{-}H4} = 7.9$ Hz, $J_{H3\text{-}H2} = 2.1$ Hz), 4.42 (H2, dd, 1H, $J_{H2\text{-}H1} = 5.2$ Hz, $J_{H2\text{-}H3} = 2.5$ Hz), 4.24 (H4, dd, 1H, $J_{H4\text{-}H3} = 8.0$ Hz, $J_{H4\text{-}H5} = 2.0$ Hz), 3.64 (H5, dd, 1H, $J_{H5\text{-}H6} = 6.9$ Hz, $J_{H5\text{-}H4} = 2.1$ Hz), 2.94 (H6, m, 1H), 2.01–1.93 (H7, m, 1H), 1.57 (CH_3, s, 3H), 1.50 (CH_3, s, 3H), 1.42 (CH_3*2, s, 6H), 1.10 (H8, d, 3H, $J_{H8\text{-}H7} = 7.0$ Hz), 0.98 (H8', d, 3H, $J_{H8'\text{-}H7} = 6.9$ Hz). MS calcd for $C_{17}H_{27}F_3NO_6$ $(M+H)^+$ 398.1. Found, 398.1.

Preparation of 6-Trifluoroacetylamino-7-*C*-methyl-6,7,8-trideoxy-2,3,4-tri-*O*-acetyl-L-*glycero*-α-D-*galacto*-1,5-octopyranosyle Bromide (22-L-*glycero*)

To a solution of **21**-L-*glycero* (990 mg, 2.26 mmol) at 0°C was added aqueous TFA (80%, 20 mL) and the reaction was stirred at rt for 1 h. After that time, the reaction mixture was concentrated and coevaporated with toluene (3 × 20 mL),

affording the desired deprotected galactose as a white solid (97%, 766 mg), used directly in the next step. MS calcd for $C_{11}H_{19}F_3NO_6$ $(M+H)^+$ 318.1. Found, 318.1.

The solid (766 mg, 2.41 mmol) was dissolved in dry CH_2Cl_2 (30 mL), and Et_3N (3.36 mL, 24.1 mmol) was injected followed by addition of Ac_2O (1.60 mL, 16.87 mmol) and DMAP (30 mg, 0.24 mmol). The resulting reaction mixture was stirred at rt for 2 h, then quenched with MeOH (5 mL). Next, Et_2O (50 mL) was added and the resulting solution was washed with H_2O (2 × 30 mL), 1.0 N HCl (30 mL), sat. aq. $NaHCO_3$ (30 mL), and brine (30 mL). The organic layer was dried over anh. Na_2SO_4 and concentrated, yielding the desired acetylated product (89%, 1.08 g). MS calcd for $C_{19}H_{27}F_3NO_{10}$ $(M+H)^+$ 486.1. Found, 486.1.

The crude product (1.04 g, 2.13 mmol) was dissolved in dry CH_2Cl_2 (25 mL) and cooled down to 0°C, and a solution of HBr in acetic acid (33%, 6.0 mL) was added. The resulting reaction mixture was stirred at 0°C for 30 min then warmed to rt and stirred for an additional 4 h. Next, CH_2Cl_2 (50 mL) was added and the resulting solution was washed successively with a cold H_2O (2 × 10 mL), cold 50% aq. $NaHCO_3$ (2 × 10 mL), and cold brine (30 mL). The organic layer was dried over Na_2SO_4 and concentrated to yield the desired **22**-$_L$-glycero (882 mg, 70% from **21**-$_L$-glycero). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.85 (H1, d, 1H, $J_{H1\text{-}H2}$ = 4.9 Hz), 4.75 (H3, dd, 1H, $J_{H3\text{-}H4}$ = 8.0 Hz, $J_{H3\text{-}H2}$ = 1.9 Hz), 4.50–4.45 (H2, H4, m, 2H), 4.05 (H5, dd, 1H, $J_{H5\text{-}H6}$ = 7.0 Hz, $J_{H5\text{-}H4}$ = 1.9 Hz), 2.99 (H6, m, 1H), 2.09–1.99 (H7, m, 1H), 2.02 (CH_3, s, 9H), 0.95 (H8, d, 3H, $J_{H8\text{-}H7}$ = 6.9 Hz), 0.93 (H8', d, 3H, $J_{H8'\text{-}H7}$ = 7.0 Hz). MS calcd for $C_{17}H_{24}BrF_3NO_8$ $(M+H)^+$ 507.2. Found, 507.2.

Preparation of 6-Trifluoroacetylamino-7-*C*-methyl-6,7,8-trideoxy-2,3,4-tri-*O*-acetyl-L-*glycero*-α-D-*galacto*-1,5-octopyranosyle Chloride (23-$_L$-*glycero*)

To a solution of **22**-$_L$-*glycero* (800 mg, 1.58 mmol) in AcOH (18 mL) at rt AgOAc (260 mg, 1.58 mmol) was added. After 1 h reaction time, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and washed with H_2O (20 mL), aq. $NaHCO_3$ (20 mL), and brine (20 mL). Organic phase was dried (Na_2SO_4) and concentrated to give acetylated product as yellow oil (720 mg). The crude product (700 mg, 1.48 mmol) was dissolved in CH_2Cl_2 (15 mL) and PCl_5 (322 mg, 1.55 mmol) was added in one portion, followed by $BF_3{\bullet}OEt_2$ (10 μL). The resulting reaction mixture was stirred for 1 h, diluted with CH_2Cl_2 (30 mL), and washed with sat. aq. $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, yielding **23-$_L$-*glycero*** (657 mg, 90%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 5.95 (H1, d, 1H, $J_{H1\text{-}H2}$ = 5.2 Hz), 4.80 (H3, dd, 1H, $J_{H3\text{-}H4}$ = 7.8 Hz, $J_{H3\text{-}H2}$ = 1.9 Hz), 4.51–4.44 (H2, H4, m, 2H), 4.00 (H5, dd, 1H, $J_{H5\text{-}H6}$ = 7.2 Hz, $J_{H5\text{-}H4}$ = 2.0 Hz), 3.01 (H6, m, 1H), 2.11–2.05 (H7, m, 1H),

2.01 (CH_3, s, 9H), 0.90 (H8, d, 3H, $J_{H8\text{-}H7} = 7.0$ Hz), 0.88 (H8', d, 3H, $J_{H8'\text{-}H7} = 6.8$ Hz). MS calcd for $C_{17}H_{24}ClF_3NO_8$ $(M+H)^+$ 462.1. Found, 462.1.

Preparation of Methyl 6-Trifluoroacetylamino-7-*C*-methyl-6,7,8-trideoxy-2,3,4-tri-*O*-acetyl-1-thio-L-*glycero*-α-D-*galacto*-1,5-octopyranoside (24-$_L$-*glycero*)

The crude **23**-$_L$-*glycero* (620 mg, 1.34 mmol) was dissolved in DMF (10 mL) and HMPA (1.25 mL) was added, followed by MeSNa (280 mg, 4.02 mmol). The resulting reaction mixture was stirred for 1 h and partitioned between Et_2O (50 mL) and 1:1 H_2O:brine (20 mL). The layers were separated, and the aqueous layer was washed with Et_2O (50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated. The residue was dissolved in CH_2Cl_2 (30 mL) and treated with Et_3N (1.86 mL, 13.4 mmol), Ac_2O (0.88 mL, 9.40 mmol), and DMAP (16 mg, 0.13 mmol). After 1 h the reaction was quenched with MeOH (5.0 mL) and partitioned between Et_2O (15 mL) and H_2O (15 mL). The layers were separated, and the organic layer was washed with 1.0 M aq. HCl (20 mL), sat. aq. $NaHCO_3$ (20 mL), and brine (20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The crude product was filtered through a short pad of silica gel using, as eluent, 10% EtOAc in hexane. The desired **24**-$_L$-*glycero* was obtained after concentration of the solvent as colorless viscous oil (318 mg, 50%). ^1H NMR ($CDCl_3$, 400 MHz): δ_H 5.50 (H1, d, 1H, $J_{H1\text{-}H2} = 5.7$ Hz), 4.78 (H3, dd, 1H, $J_{H3\text{-}H4} = 8.0$ Hz, $J_{H3\text{-}H2} = 2.1$ Hz), 4.59–4.50 (H2, H4, m, 2H), 4.05 (H5, dd, 1H, $J_{H5\text{-}H6} = 7.0$ Hz, $J_{H5\text{-}H4} = 1.8$ Hz), 3.10 (H6, m, 1H), 2.20–2.12 (H7, m, 1H), 2.08 (CH_3, s, 3H), 1.99 (CH_3, s, 9H), 1.00 (H8, d, 3H, $J_{H8\text{-}H7} = 7.2$ Hz), 0.97 (H8', d, 3H, $J_{H8'\text{-}H7} = 6.8$ Hz). MS calcd for $C_{18}H_{27}F_3NO_8S$ $(M+H)^+$ 474.1. Found, 474.1.

Preparation of Methyl 6-Amino-7-*C*-methyl-6,7,8-trideoxy-1-thio-L-*glycero*-α-D-*galacto*-1,5-octopyranoside (25-$_L$-*glycero*), the Carbohydrate Core of Antibiotic 6-epi VIC 10555

The protected **24**-$_L$-*glycero* (290 mg, 0.61 mmol) was dissolved in MeOH (15 mL) and 1.0 M aq. NaOH (6.1 mL, 6.1 mmol) was added. The resulting reaction mixture was stirred for 2 h, then acidified to pH 2 with 1.0 M aq. HCl. After evaporation of the solvents the residue was dissolved in EtOH (10 mL) and filtered through a medium-porosity glass frit (to remove NaCl). The filtrate was treated with Amberlite IRA-400 resin (15 mL resin bed in MeOH). The resulting mixture was stirred at rt for 2 h and then filtered. The resin was washed with MeOH (3 · 10 mL) and the filtrate concentrated in vacuo to give the totally deprotected **25**-$_L$-*glycero* as white foam (138 mg, 90%). ^1H NMR (CD_3OD, 400 MHz): δ_H 5.30 (H1, d, 1H, $J_{H1\text{-}H2} = 5.7$ Hz), 4.25 (H3, dd, 1H, $J_{H3\text{-}H4} = 8.0$ Hz, $J_{H3\text{-}H2} = 2.1$ Hz), 4.10–3.99 (H2, H4, m, 2H), 3.90 (H5, dd,

1H, $J_{H5\text{-}H6} = 7.5$ Hz, $J_{H5\text{-}H4} = 1.9$ Hz), 3.30 (H6, m, 1H), 2.89–2.79 (H7, m, 1H), 2.08 (CH_3, s, 3H), 1.00 (H8, d, 3H, $J_{H8\text{-}H7} = 7.0$ Hz), 0.99 (H8', d, 3H, $J_{H8'\text{-}H7} =$ 6.9 Hz). MS calcd for $C_{10}H_{22}NO_4S$ $(M+H)^+$ 252.1. Found, 252.1.

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