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Total Synthesis of α-1C-Galactosylceramide, an Immunostimulatory C-Glycosphingolipid, and Confirmation of the Stereochemistry in the First-Generation Synthesis

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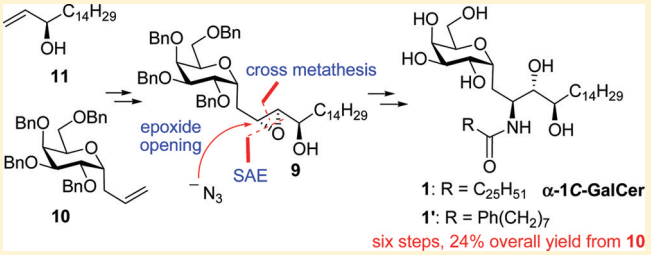
Supporting Information

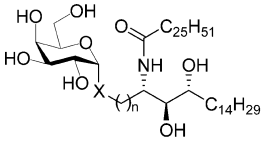
ABSTRACT: A nonisosteric α-*C*-glycoside analogue of KRN7000 (α-1*C*-GalCer, **1**) was reported to induce a selective type of cytokine release in human invariant natural killer cells in vitro. We report here a very concise synthetic route to **1** and its analogue **1′**. The key steps include olefin cross-metathesis, Sharpless asymmetric epoxidation, and epoxide opening by NaN_3/NH_4Cl. Inversion of configuration at the amide-bearing carbon in the phytosphingosine backbone constructed by epoxide opening in our previous synthesis of **1** was verified, indicating that remote group participation is not involved during the epoxide-opening reaction.



INTRODUCTION

(2′*S*,3′*S*,4′*R*)-2′-*N*-Hexacosanoylamino-3′,4′-dihydroxyoctadecyl-α-*C*-D-galactopyranoside (α-1*C*-GalCer, **1**, Chart 1),[1] α-galactosylceramide (**2**),[2] and α-*C*-galactosylceramide (**3**)[3] are synthetic glycolipids that bind to a cell surface protein, CD1d, to activate invariant natural killer T (iNKT) cells. Stimulated iNKT cells produce cytokines that regulate a wide range of immune responses. An important challenge in the field of synthetic glycosphingolipid research is the development of ligands that selectively polarize the NKT cell response toward the secretion of either Th1-type (such as interferon-γ, IFN-γ) or Th2-type (such as IL-4 and IL-13) cytokines since secretion of either type of cytokine (but not both types simultaneously) may be useful in disease treatment.

Chart 1. Structures of KRN7000 (2) and *C*-Glycoside Analogues 1 and 3



1 X = CH_2 n = 0 (α-1*C*-GalCer)
2 X = O n = 1 KRN7000 (α-GalCer)
3 X = CH_2 n = 1 (α-*C*-GalCer)

In 2006, we reported that **1** induced higher ratios of IFN-γ:IL-4 and IFN-γ:IL-13 than **2** and **3** in human iNKT cells.[1] From the view of synthesis, **1** is structurally similar to unnatural *C*-linked glycopeptides,[4] which also feature a *C*-glycosidic bond and are synthetically challenging when the carbon chain linking the *C*-glycoside and the amino acid is shorter than three carbons.[5] To circumvent this limitation, we considered that the internal alkene introduced into the linker region in previous synthetic routes to *C*-glycosylpeptides, instead of being hydrogenated, can be functionalized into the amino alcohol moiety in **1**. This approach led to our previous synthesis of **1** in 2006.

The synthesis requires construction of three contiguous stereocenters in the phytosphingosine backbone; the key steps in our previous route to **1** included Sharpless asymmetric epoxidation (SAE)[6] and an epoxide-opening reaction with sodium azide under chelation-controlled conditions.[1] However, there are three problems in this synthetic route that still need to be addressed. First, in the SAE reaction, an epimeric mixture (1:1) of allylic propargylic alcohols was used;[7] thus the maximum yield of this step is 50%. Obviously, it would be much more efficient if one could prepare the requisite allylic propargylic alcohol epimer with a high diastereoisomeric purity to participate in the SAE reaction. Second, the yield of the azido diol product **5** formed by epoxide opening of **4** with NaN_3/NH_4Cl was poor because **5** was transformed into bicyclic triazole **6** (30%) via an intramolecular alkyne−azide cycloaddition[8] (without catalysis by copper, Scheme 1). Attempts to control the reaction time to maximize the yield of **5** prior to the formation of **6** were unsuccessful because the R_f values of reactant **4** and product **5** are nearly identical. An effort to prevent the formation of **6** by lowering the temperature also failed, leading to almost complete recovery of **4**. Third, there is an unresolved question[9] concerning the stereochemical course

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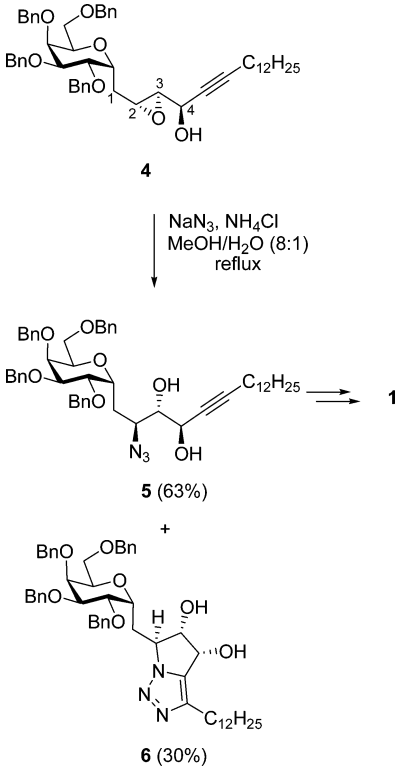
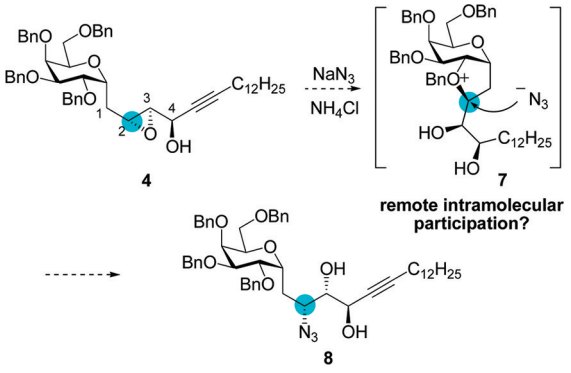
Scheme 1. Opening of Epoxide 4 and Formation of Bicyclic Triazole 6



of the azide-mediated epoxide opening of **4**; in a synthetic route to **3**, Pu and Franck disclosed a "retention" phenomenon during the opening of an α-hydroxy epoxide using Ti(O-*i*Pr)$_2$(N$_3$)$_2$.[10,11] Retention of configuration might occur via remote group participation.[12] Therefore, we decided to investigate the possibility of intramolecular participation by the 2′-*O*-benzyl group to form oxonium ion intermediate **7** (Scheme 2), which on attack by the azide ion would form amino diol **8** with retention of configuration.

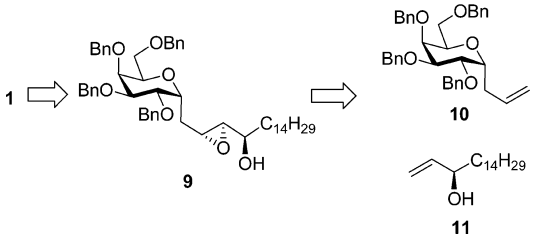
Scheme 2. Possible Mechanism of Retention in the Opening of Epoxide 4



Given the importance of the absolute configuration of the amide-bearing carbon of the phytosphingosine backbone of glycosphingolipid antigens,[10,13] clarification of this stereochemical problem is necessary in the investigation of structure–activity relationships. Herein, we report the development of a more concise and practical route to **1**, which will allow us to make a larger quantity of analogue **1** available to the immunology community. We also confirmed that the epoxide-opening reaction of **4** with sodium azide proceeded with inversion of configuration in the first-generation synthesis.

The retrosynthetic plan for the second-generation synthesis of **1** is outlined in Scheme 3. As in our previous synthesis of **1**,

Scheme 3. Retrosynthetic Plan to 1



we hypothesized that epoxy alcohol **9** might serve as a synthetic precursor of **1** through four straightforward transformations: (i) epoxide opening by azide anion, (ii) reduction of the resulting azide to the corresponding amine, (iii) N-acylation with a fatty acid, and (iv) global deprotection. A noteworthy modification is the absence of the alkyne moiety in the phytosphingosine chain; thus, the azido diol resulting from the epoxide opening of **9** in the new synthetic route would not undergo an intramolecular azide–alkyne click reaction. In turn, **9** can be obtained from an allylic alcohol via SAE, which can be disconnected into the simpler synthons, allylic alcohol **11** and α-*C*-allyl tetra-*O*-benzylglycoside **10**, by olefin cross-metathesis (CM).[14] Because **11** can be prepared in high enantiomeric purity,[15] SAE will not suffer from the same problem of 50% maximum yield as was encountered under the kinetic resolution condition in our previous synthesis of **1**.

RESULTS AND DISCUSSION

Second-Generation Synthesis of 1 and 1′. Our new synthesis commenced with the preparation of the chain partner of CM, alkene **11**, which was obtained in high yield (86%, two steps) by Wittig methylenation of aldehyde **13** (synthesized from 1-hexadecene (**12**) in four steps and 50% overall yield)[15] followed by deprotection of the PMB group under acidic conditions (Scheme 4). α-*C*-Allyl tetra-*O*-benzylgalactoside **10** has already been used as a valuable synthon in CM;[16] it was obtained in 91% yield by allylation of methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranoside with allyltrimethylsilane using a literature procedure.[17] Furthermore, Grubbs and co-workers demonstrated the utility of α-*C*-allyl tetra-*O*-benzylglucoside, the glucosyl counterpart of **10**, in CM with alkenes.[14] To our delight, we found that refluxing allylic alcohol **11** with an excess of galactosyl olefin **10** (3.0 equiv) in the presence of 10 mol % (relative to **11**) of Grubbs–Hoveyda second-generation catalyst (**15**)[18] led to formation of CM product **17** in 63% isolated yield. The *E* configuration of the alkene moiety in **17** was confirmed by the coupling constant of the vinylic protons (J = 15.4 Hz). Several attempts to improve the yield of **17** were unsuccessful. For example, we found that CM between **10** and PMB-protected allylic alcohol **14** in a 1:3 molar ratio with 25 mol % (relative to **10**) of Grubbs second-generation catalyst (**G2**) afforded the desired heterodimer **16** in only 34% yield, along with the homodimer of **10** in ~28% yield. Reaction of **11** with **10** in a 4:1 molar ratio and 17 mol % of **G2** catalyst (relative to **10**) at 45 °C for 21 h provided the desired product **17** in only 38% yield; changing the catalyst from **G2** to **15**

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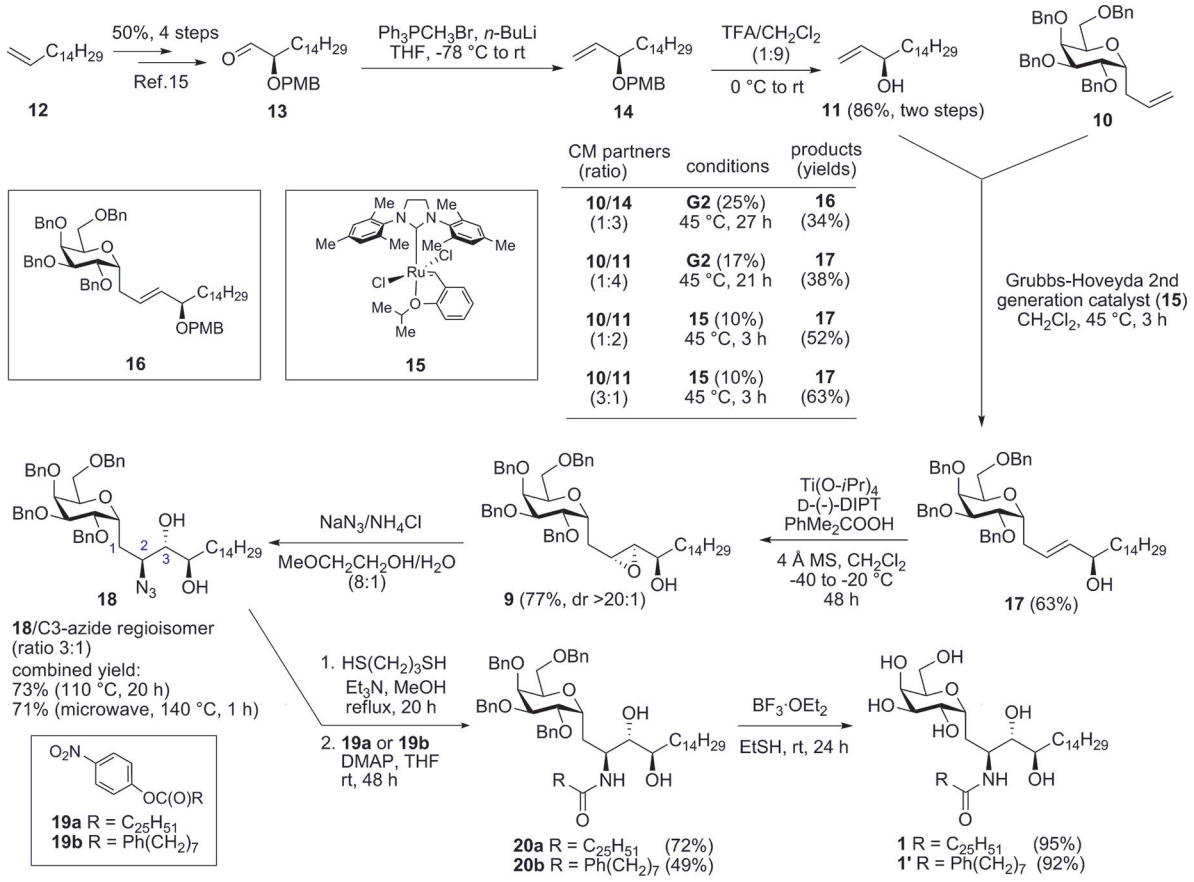
Scheme 4. Synthesis of 1 and 1′

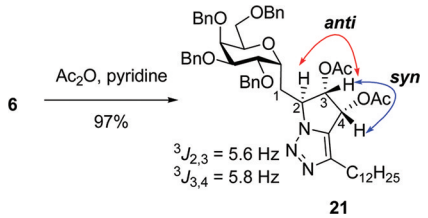


improved the yield of **17** to 52%. Increasing the ratio of **11**/**10** did not improve the yield.

SAE of **17** provided epoxy alcohol **9** in 77% yield. The diastereoisomeric purity of **9** was determined to be high (dr >20:1) by preparing the corresponding (*S*)-MTPA ester derivative.[19] Epoxide opening of **9** under Sharpless conditions[20] (20 equiv of NaN_3, 10 equiv of NH_4Cl, methoxyethanol/H_2O, 110 °C, 20 h) delivered a mixture of azido diol **18** and its C-3 azide regioismer in a ratio of 3:1 and a combined 73% yield,[21] whereas at the temperature of refluxing MeOH/H_2O, there was almost complete recovery of reactant **9**. Microwave-assisted opening of epoxide **9** afforded **18** in about the same yield (71%) but within a much shorter time period (1 h). Unlike the epoxide-opening reaction of **4** in our previous synthesis,[1] reactant **9** and product **18** have different R_f values (hexane/EtOAc 3:1); thus the reaction can be monitored by TLC. Azide **18** was smoothly converted to the corresponding amine with 1,3-propanedithiol as the reducing agent,[22] and in situ N-acylation with *p*-nitrophenyl hexacosanoate (**19a**) afforded amide **20a** (72%, two steps). Because Wong and co-workers[23] reported that introduction of a terminal phenyl group into the amide chain of **2** led to an enhanced production of IFN-γ, we also prepared amide **20b** (49%, two steps) by N-acylation with *p*-nitrophenyl 8-phenyloctanoate (**19b**). The target compounds **1** and **1′** were obtained by BF_3·OEt_2/EtSH[24]-mediated deprotection of the *O*-benzyl groups in almost quantitative yield (95 and 92%, respectively). The new route consists of only six steps from α-*C*-allyl tetra-*O*-benzylglycoside **10** and proceeded in an overall yield of 24% (compared with nine steps and 11% overall yield in our previous synthesis).[1]

Confirmation of the Stereochemistry in the First-Generation Synthesis of 1. The stereochemistry of the phytosphingosine backbone in **2** strongly affects its bioactivity; inversion of the configuration of the amide-bearing carbon gives an analogue that failed to activate iNKT cells to produce cytokines.[13a] To investigate the relative configurations in the phytosphingosine backbone of **1**, we initially attempted to analyze the coupling constants in bicyclic triazole **21** prepared from diol **6**. As shown in Scheme 5, $^3J_{3,4}$ and $^3J_{2,3}$ in **21**, which

Scheme 5. Synthesis of 21 from 6



should have *syn* and *anti* relations, respectively, under the scenario of inversion, surprisingly have almost the same coupling constants ($^3J_{3,4}$ = 5.8 Hz and $^3J_{2,3}$ = 5.6 Hz), and H-3 displays a triplet-like signal.[25] The flexibility of five-membered rings makes the NMR coupling constants of vicinal protons of little value in the assignment of relative configurations, and, indeed, $^3J_{syn}$ can be larger or smaller than $^3J_{anti}$.[26] Therefore, our evidence of ^3J values in **21** alone is unclear with respect to the configuration at C-2. Unfortunately, the fact that the key

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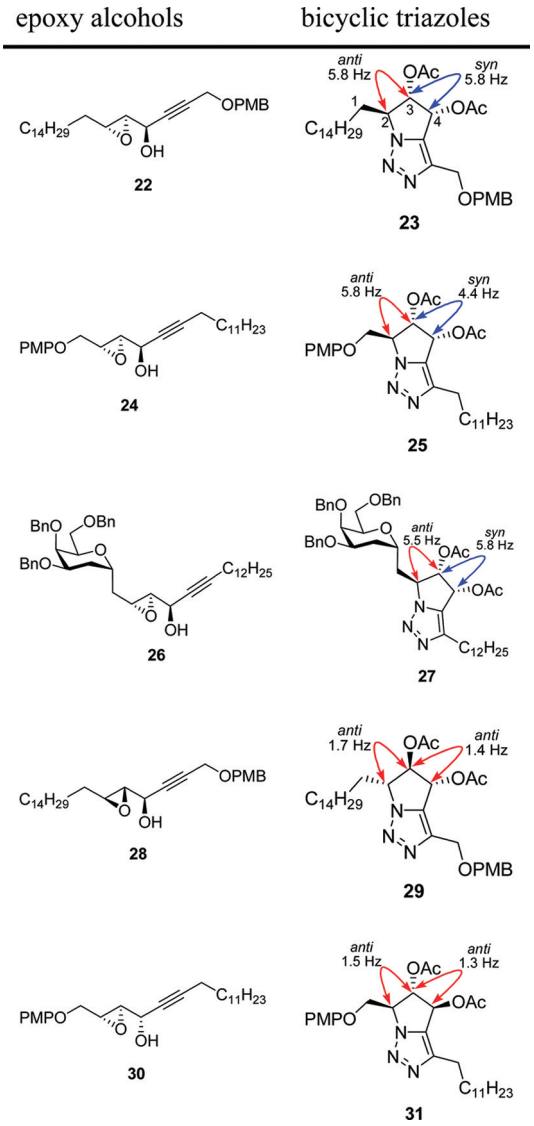
proton at C-2 position in **21** overlapped with the protons in the galactose moiety rendered an NOE investigation impossible.

Therefore, we decided to explore the stereochemical relationships of several model bicyclic triazole compounds generated from epoxy alcohols through the same sequence of reactions. The results are summarized in Table 1. It is

Table 1. ^3J Values in Bicyclic Triazoles[a]



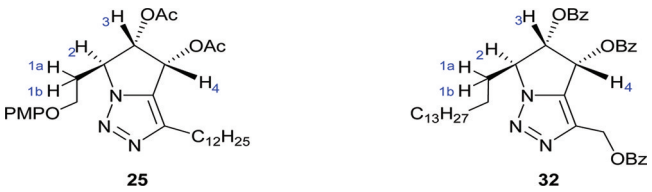
[a]See ref 31 for the preparation of **24**, **25**, **30**, and **31**; for the preparation of the other compounds, see Schemes S5, S6, and S7 in the Supporting Information.

reasonable that *cis*-epoxy alcohols **28** and **30** were converted to bicyclic triazoles **29** and **31** with almost the same $^3J_{2,3}$ (1.7, 1.5 Hz) and $^3J_{3,4}$ (1.4, 1.3 Hz) values, which both have a *anti* relationship. However, like their sugar counterpart **21**, bicyclic triazoles **23**, **25**, and **27**, which were obtained from *trans*-epoxy alcohols **22**, **24**, and **26**, respectively, again show almost identical $^3J_{2,3}$ (5.8, 5.8, 5.5 Hz) and $^3J_{3,4}$ (5.8, 4.4, 5.8 Hz) values, which are *anti* and *syn* relations, respectively.

In order to avoid the possibility of remote-group participation in the epoxide-opening reaction, we prepared 2′-deoxy epoxide **26**, which does not contain a 2′-*O*-benzyl group. The bicyclic triazole derivative **27** obtained from **26** exhibited the same pattern of ^3J values as **21**. Therefore, participation of the 2′-*O*-benzyl group in **4** appears not to be involved in the epoxide opening of **4** with NaN_3/NH_4Cl.

However, we have still not excluded the possibility that retention of configuration at the azide-bearing carbon may have taken place via a mechanism similar to the Ti-catalyzed epoxide opening/intramolecular delivery of azide from the Ti(IV) complex as suggested by Tan et al.[27] To the best of our knowledge, only one example of retention of epoxide opening has been reported with NaN_3/NH_4Cl,[28] but the mechanism involves neighboring group participation of the d electrons on iron, which is not applicable in the present reaction. Therefore, we carried out 2D NOESY experiments with **25** in order to assign the relative configuration at the C-2 position. As shown in Table 2, the NOE correlation of H-3 and H-1b is greater

Table 2. Key NOE Correlations in Bicyclic Triazoles 25 and 32[a]



	cross-peak integrals					
	25			32		
	mixing time					
proton pair	300 ms	500 ms	700 ms	300 ms	500 ms	700 ms
H-4/H-3	1.00	1.00	1.00	1.00	1.00	1.00
H-4/H-2	NO	0.06	NO	NO	0.11	NO
H-4/H-1a	NO	NO	NO	NO	NO	NO
H-4/H-1b	NO	NO	NO	NO	NO	NO
H-3/H-2	0.34	0.33	0.27	0.28	0.31	0.25
H-3/H-1a	0.05	0.13	0.07	0.25	0.22	0.18
H-3/H-1b	0.41	0.39	0.40	0.42	0.37	0.31

[a]The integral of the H-4/H-3 cross-peak was used as the internal calibrant (its integral was set to 1.00). NO, not observed.

than that of H-3 and H-2, indicating that H-3 and H-1a/H-1b are on the same side of the bicyclic ring. Since the NOE correlation of H-4 and H-3 is greater than that of H-3 and H-2, we conclude that H-3 and H-4 have a *syn* relationship, and thus H-2 and H-3 are *anti*. It is noteworthy that when a 500 ms mixing time was used, a weak NOESY cross-peak between H-4 and H-2 is observed, whereas no cross-peak of H-4 and H-1a (or H-4 and H-1b) is observed (see Supporting Information). In order to determine the configuration at the C-2 position, we conducted 2D NOESY experiments with different mixing times (700, 500, and 300 ms). In this progression, the intensity of the NOE signals should decrease with a decrease in mixing time, and the artifacts tend to disappear as the mixing time decreases.[29] The H-2/H-4 cross-peak integrated intensity disappeared in the spectra recorded with the 300 and 700 ms mixing times (Table 2). Therefore, we consider the H-2/H-4 cross-peak at the 500 ms mixing time to be an artifact. Thus, we conclude that H-2 is on the opposite side of the bicyclic ring to H-3 and H-4.

In view of the high degree of flexibility of five-membered rings[26] and the small difference in the ^3J values between **25** and **21** (or **23**), we also carried out 2D NOESY experiments with

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bicyclic triazole **32**, which was prepared from epoxy alcohol **22** through the same sequence of transformations and straightforward manipulation of the protecting groups. As shown in Table 2, the pattern of NOE correlations of **32** is very similar to that of **25**. Again, we identified an artifact between H-4 and H-2 in the 500 ms mixing time NOESY spectrum that was absent in the other NOESY spectra.[30] According to the analysis of NOE correlations of **25** and **32** shown in Table 2, we conclude that opening of *trans*-epoxy alcohols including **4** with NaN_3/NH_4Cl proceeds with inversion of configuration and not with retention.[31]

■ CONCLUSION

In summary, we have achieved a concise total synthesis of **1** and **1′** in only six steps from α-*C*-allyl tetra-*O*-benzylglycoside **10** and allylic alcohol **11** and 24% overall yield, using CM with the Grubbs–Hoveyda second-generation catalyst. The absence of the alkyne group in the phytosphingosine chain of azido diol **18** circumvents the intramolecular azide–alkyne click reaction that generated byproduct **6** in the first-generation synthesis, which employed azido diol **5**. Since the assignment of the relative stereochemistry of the N_3-bearing carbon in **5** from analysis of the vicinal coupling constants ($^3J_{2,3}$ and $^3J_{3,4}$) of bicyclic triazole **21** was inconclusive, we analyzed the configuration of model compounds **25** and **32** using 2D NOESY with different mixing times and verified that opening of epoxide **4** with NaN_3 and NH_4Cl proceeds with inversion of configuration.

■ EXPERIMENTAL SECTION

All reactions were carried out under a dry nitrogen atmosphere using oven-dried glassware and magnetic stirring. The solvents were dried as follows: THF was heated at reflux over sodium benzophenone ketyl; toluene was heated at reflux over sodium; CH_2Cl_2 was dried over CaH_2. Anhydrous iPr$_2$NEt, CH_3CN, Et_3N, and benzene were used directly as purchased. Silica gel 60 F254 aluminum TLC plates of 0.2 mm thickness were used to monitor the reactions. The spots were visualized with short wavelength ultraviolet light or by charring after spraying with 15% H_2SO_4. Flash chromatography was carried out with silica gel 60 (230–400 ASTM mesh). ^{1}H NMR spectra were obtained on 400 or 500 MHz spectrometers. Chemical shifts were referenced on residual solvent peaks: $CDCl_3$ (δ = 7.26 ppm for ^{1}H NMR and 77.00 ppm for ^{13}C NMR). Optical rotations were measured at rt in a 1.0 dm cell. High-resolution mass spectra were acquired by electrospray ionization.

(3*R*)-*O*-(4′-Methoxybenzyl)-1-heptadecen-3-ol (14) and (3*R*)-1-Heptadecen-3-ol (11). To a stirred suspension of Ph_3PCH_3Br (3.70 g, 10.4 mmol) in anhydrous THF (100 mL) was added *n*-BuLi (4.10 mL, 2.5 M in hexane, 10.4 mmol) dropwise at −78 °C. The mixture was stirred for 3 h at −78 °C. A solution of aldehyde **13**[15] (3.00 g, 7.97 mmol) in 20 mL of THF was added slowly. The mixture was stirred overnight, during which time the temperature was increased slowly from −78 °C to rt. Then 300 mL of hexane was added. The mixture was passed through a pressed pad of Celite, which was rinsed with hexane/EtOAc (300 mL, 10:1). The filtrate was concentrated under reduced pressure to provide the crude PMB-protected alkene **14**, which was dissolved in CH_2Cl_2 (80 mL). TFA (9 mL, 0.12 mol) was added slowly at 0 °C. The reaction mixture was stirred at rt for 10 min, and then the reaction was quenched by dropwise addition of saturated aqueous $NaHCO_3$ solution (*caution*: CO_2 is released). The resultant neutral biphasic mixture was transferred to a separatory funnel. The aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 15:1) provided allylic alcohol **11** (2.34 g, 86%, two steps). Data for **14**: $[\alpha]_D^{28}$ +19.5 (*c* 0.48, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.20–1.50 (m, 24H), 1.57–1.67 (m, 2H), 3.68 (q, *J* = 6.9 Hz, 1H), 3.80 (s, 3H), 4.28 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 5.16–5.23 (m, 2H), 5.72 (ddd, *J* = 7.9, 10.3, 17.4 Hz, 1H), 6.85–6.89 (m, 2H), 7.23–7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.4, 29.4, 29.53, 29.58, 29.61, 29.65, 29.67, 29.69, 31.9, 35.5, 55.2, 69.6, 80.3, 113.7, 116.9, 129.3, 130.9, 139.3, 159.0; ESI-HRMS $[M + NH_4]^+$ calcd for *m*/*z* $C_{25}H_{46}NO_2^+$ 392.3523, found 392.3523. Data for **11**: $[\alpha]_D^{27}$ −7.0 (*c* 0.6, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.20–1.42 (m, 24H), 1.46–1.59 (m, 2H), 4.09 (q, *J* = 6.4 Hz, 1H), 5.09 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.21 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.86 (ddd, *J* = 6.3, 10.4, 17.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.3, 29.3, 29.54, 29.57, 29.64, 29.66, 29.67, 31.9, 37.0, 73.2, 114.5, 141.3; ESI-HRMS $[M + Na]^+$ calcd for *m*/*z* $C_{17}H_{34}NaO^+$ 277.2502, found 277.2501.

(4′*R*,2′*E*)-4′-(4″-Methoxybenzyloxy)]-2′-octadecenyl-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (16). A mixture of **10**[17] (46 mg, 0.081 mmol) and **14** (82 mg, 0.219 mmol) was dissolved in CH_2Cl_2 (5 mL). The solution was degassed by three freeze–pump–thaw cycles. After Grubbs second-generation catalyst (18 mg, 0.021 mmol) was added in one portion, the reaction mixture was stirred at 45 °C for 27 h and was then reduced in volume to 1 mL under reduced pressure. Purification by flash chromatography on silica gel (PhMe/EtOAc 10:1, 8:1 to 6:1) provided **16** (25 mg, 34%) as a clear oil. Data for **16**: $[\alpha]_D^{29}$ +34.5 (*c* 1.35, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.15–1.44 (m, 24H), 1.53–1.64 (m, 2H), 2.32–2.50 (m, 2H), 3.56–3.62 (m, 1H), 3.65–3.70 (m, 1H), 3.71–3.85 (m, 6H), 3.98–4.07 (m, 3H), 4.21 (d, *J* = 11.5 Hz, 1H), 4.40–4.77 (m, 9H), 5.36 (dd, *J* = 8.3, 15.4 Hz, 1H), 5.49 (dt, *J* = 15.4, 6.9 Hz, 1H), 6.81–6.86 (m, 2H), 7.19–7.23 (m, 2H), 7.23–7.35 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 29.4, 29.59, 29.65, 29.7, 31.9, 35.7, 55.2, 67.2, 69.1, 72.1, 72.9, 73.1, 73.2, 74.2, 76.3, 79.4, 113.6, 127.4, 127.5, 127.6, 127.8, 127.9, 128.26, 128.33, 128.4, 129.3, 130.1, 131.0, 133.4, 138.21, 138.24, 138.45, 138.51, 158.9; ESI-HRMS $[M + NH_4]^+$ calcd for *m*/*z* $C_{60}H_{82}NO_7^+$ 928.6086, found 928.6089.

(4′*R*,2′*E*)-4′-Hydroxy-2′-octadecenyl-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (17). A mixture of **10**[17] (160 mg, 0.283 mmol) and **11** (24 mg, 0.094 mmol) was dissolved in CH_2Cl_2 (5 mL). The solution was degassed by three freeze–pump–thaw cycles. After Grubbs–Hoveyda second-generation catalyst (6 mg, 0.001 mmol) was added in one portion, the reaction mixture was stirred at 45 °C for 3 h and was then reduced in volume to 1 mL under reduced pressure. Purification by flash chromatography on silica gel (PhMe/EtOAc 8:1, 7:1 to 6:1) provided allylic alcohol **17** (47 mg, 63%) as a colorless wax: $[\alpha]_D^{29}$ +24.9 (*c* 2.3, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.16–1.44 (m, 24H), 1.45–1.55 (m, 2H), 1.88 (s, 1H), 2.27–2.44 (m, 2H), 3.54 (dd, *J* = 3.6, 10.4 Hz, 1H), 3.72 (dd, *J* = 2.7, 7.2 Hz, 1H), 3.75–3.83 (m, 2H), 3.92–4.04 (m, 4H), 4.43–4.75 (m, 8H), 5.47 (dd, *J* = 6.5, 15.4 Hz, 1H), 5.52 (dt, *J* = 6.3, 15.4 Hz, 1H), 7.23–7.35 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.6, 25.4, 29.3, 29.57, 29.61, 29.65, 31.9, 36.9, 67.8, 70.8, 72.2, 72.96, 72.99, 73.2, 74.2, 76.3, 127.4, 127.53, 127.60, 127.71, 127.77, 127.82, 127.85, 127.90, 128.2, 128.3, 135.6, 138.0, 138.2, 138.3, 138.5; ESI-HRMS $[M + NH_4]^+$ calcd for *m*/*z* $C_{52}H_{74}NO_6^+$ 808.5511, found 808.5505.

(2′*R*,3′*R*,4′*S*)-1-(2′,3′-Oxiran-4′-hydroxyoctadecyl)-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (9). A mixture of activated 4 Å molecular sieves (0.5 g), D-(−)-DIPT (85 mg, 0.35 mmol), and CH_2Cl_2 (10 mL) was stirred at rt for 30 min. After the mixture was cooled to −40 °C, Ti(O-iPr)$_4$ (85 μL, 83 mg, 0.29 mmol) was added. After the resultant mixture was allowed to stir at −40 °C for 1 h, a solution of **17** (230 mg, 0.291 mmol) in 3 mL of CH_2Cl_2 was added dropwise. The reaction mixture was stirred at −40 °C for another 30 min, and cumene hydroperoxide (215 μL, 1.16 mmol, 80% technical grade) was added via syringe. The reaction mixture was stored at −20 °C without stirring for 48 h, and then 10% aqueous D-tartaric acid solution (1 mL) was added. The reaction mixture was stirred vigorously at rt for 30 min and filtered through a pressed pad of Celite. The organic layer was separated, and the aqueous layer was

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extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were concentrated under reduced pressure. The residue was dissolved in Et_2O (10 mL), and 30% aqueous NaOH solution (1 mL) was added. The biphasic mixture was stirred vigorously at 0 °C for 1 h. The organic phase was separated, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 3.5:1) afforded epoxy alcohol **9** (180 mg, 77%, dr >20:1) as a colorless oil. The dr value was determined by analysis of the corresponding (*S*)-MTPA esters:[19] $[\alpha]_D^{28}$ +41.6 (*c* 0.7, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.16−1.57 (m, 26H), 1.67−1.79 (m, 2H), 2.65 (s, 1H), 2.68 (dd, *J* = 2.1, 5.8 Hz, 1H), 2.81−2.85 (m, 1H), 3.27−3.33 (m, 1H), 3.53 (dd, *J* = 3.4, 10.6 Hz, 1H), 3.56−3.60 (m, 1H), 3.68 (dd, *J* = 2.8, 5.9 Hz, 1H), 3.94 (dd, *J* = 2.9, 4.5 Hz, 1H), 3.99−4.15 (m, 3H), 4.42−4.68 (m, 8H), 7.18−7.34 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.1, 29.3, 29.60, 29.61, 29.63, 29.67, 31.9, 34.0, 54.8, 61.5, 66.6, 70.8, 72.5, 72.7, 73.0, 73.2, 73.4, 73.9, 75.4, 76.6, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.2, 128.35, 128.36, 128.37, 128.39, 137.80, 138.84, 138.1, 138.3; ESI-HRMS $[M + NH_4]^+$ calcd for *m*/*z* $C_{52}H_{74}NO_7^+$ 824.5460, found 824.5453.

(2′*S*,3′*S*,4′*R*)-1-(2′-Azido-3′,4′-dihydroxyoctadecyl)-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (18). *Oil bath heating*: NH_4Cl (50 mg, 0.935 mmol) and NaN_3 (120 mg, 1.85 mmol) were added to epoxy alcohol **9** (100 mg, 0.124 mmol) in 9 mL of $MeOCH_2CH_2OH/H_2O$ (8/1). The reaction mixture was stirred at 110 °C for 20 h. The reaction mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc/hexane 1:4) afforded a mixture of **18** and its C-3 azide regioisomer (3:1, 77 mg, 73%). *Microwave heating*: To a solution of epoxy alcohol **9** (10 mg, 0.0124 mmol) in 1.8 mL of $MeOCH_2CH_2OH/H_2O$ (8/1) in a 10 mL microwave reaction test tube were added NH_4Cl (6.6 mg, 0.124 mmol) and NaN_3 (16 mg, 0.248 mmol). The tube was placed in a microwave reactor. The reaction was conducted at 140 °C for 1 h. The workup and purification followed the above procedure to afford a mixture of **18** and its C-3 azide regioisomer (3:1, 7.5 mg, 71%). Data for the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.15−1.34 (m, 24H), 1.35−1.50 (m, 2H), 1.92−1.99 (m, 1H), 2.18−2.26 (m, 1H), 3.32 (d, *J* = 9.8 Hz, 1H), 3.50−3.57 (m, 1H), 3.59−3.66 (m, 2H), 3.69−3.75 (m, 1H), 3.77−3.85 (m, 2H), 3.90−4.02 (m, 2H), 4.40−4.83 (m, 9H), 7.19−7.39 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.9, 29.3, 29.61, 29.63, 29.7, 31.2, 31.9, 61.1, 70.5, 72.02, 72.05, 72.6, 73.16, 73.26, 73.45, 73.65, 74.4, 76.3, 127.6, 127.7, 127.82, 127.84, 128.0, 128.05, 128.15, 128.20, 128.34, 128.40, 128.43, 137.1, 137.9, 138.0, 138.3; ESI-HRMS $[M + Na]^+$ calcd for *m*/*z* $C_{52}H_{71}N_3NaO_7^+$ 872.5184, found 872.5187.

(2′*S*,3′*S*,4′*R*)-2′-*N*-Hexacosanoylamino-3′,4′-dihydroxyoctadecyl-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (20a) and (2′*S*,3′*S*,4′*R*)-2′-*N*-8″-Phenyloctanoylamino-3′,4′-dihydroxyoctadecyl-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (20b). To a solution of azido diol **18** and its C-3 azide regioisomer (3:1, 50 mg, 0.059 mmol) in MeOH (2 mL) were added Et_3N (200 μL, 1.44 mmol) and 1,3-propanedithiol (120 μL, 1.19 mmol). The solution was heated at reflux for 20 h and allowed to cool to rt. The solvent was removed in vacuo to give a residue, which was dissolved in anhydrous THF (4 mL, solution A). Solution A was divided into two 10 mL round-bottom flasks, which were directly used in the amidation reaction. *p*-Nitrophenyl ester **19a** (46 mg, 0.089 mmol) and DMAP (0.5 mg, 4.0 μmol) were added to the first half of solution A (2 mL). After the mixture was stirred at rt for 48 h, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 3:1 to 5:2) to provide amide **20a** (25 mg, 72%, based on the mixture of **18** and its C-3 regioisomer) as a wax: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85−0.90 (m, 6H), 1.12−1.80 (m, 72H), 1.94−2.07 (m, 3H), 2.11−2.21 (m, 1H), 3.32−3.38 (m, 2H), 3.39−3.44 (m, 1H), 3.62 (dd, *J* = 2.7, 7.5 Hz, 1H), 3.77−3.81 (m, 1H), 3.83 (t, *J* = 3.0 Hz, 1H), 3.90−3.96 (m, 1H), 4.06−4.20 (m, 3H), 4.43−4.74 (m, 8H), 6.64 (d, *J* = 6.9 Hz, 1H), 7.22−7.36 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.7, 25.9, 29.3, 29.4, 29.5, 29.7, 31.9, 33.4, 36.5, 73.1, 73.2, 73.4, 127.5, 127.7, 127.9, 128.01, 128.03, 128.10, 128.37, 128.43, 128.49, 137.3, 137.90, 137.97, 138.3, 174.2; ESI-HRMS $[M + Na]^+$ calcd for *m*/*z* $C_{78}H_{123}NNaO_8^+$ 1224.9141, found 1224.9139.

To the other half of solution A (2 mL) were added *p*-nitrophenyl ester **19b** (46 mg, 0.135 mmol) and DMAP (0.5 mg, 4.0 μmol). After the mixture was stirred at rt for 48 h, the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (hexane/EtOAc 2:1) to provide amide **20b** (15 mg, 49%, based on the mixture of **18** and its C-3 regioisomer) as a wax: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.12−1.74 (m, 36H), 1.93−2.03 (m, 3H), 2.12−2.20 (m, 1H), 2.57 (t, *J* = 7.7 Hz, 2H), 3.32−3.43 (m, 3H), 3.62 (dd, *J* = 2.8, 7.5 Hz, 1H), 3.77−3.81 (m, 1H), 3.83 (t, *J* = 3.0 Hz, 1H), 3.89−3.97 (m, 1H), 4.06−4.19 (m, 3H), 4.43−4.74 (m, 8H), 6.63 (d, *J* = 6.9 Hz, 1H), 7.14−7.36 (m, 25H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 29.4, 29.67, 29.71, 31.9, 35.9, 72.1, 73.1, 73.3, 73.4, 74.1, 127.5, 127.7, 127.86, 127.88, 127.98, 128.00, 128.1, 128.2, 128.37, 128.42, 128.43, 128.49, 137.4, 137.9, 138.0, 138.3, 142.8, 174.1; ESI-HRMS $[M + Na]^+$ calcd for *m*/*z* $C_{66}H_{91}NNaO_8^+$ 1048.6637, found 1048.6643.

(2′*S*,3′*S*,4′*R*)-2′-*N*-Hexacosanoylamino-3′,4′-dihydroxyoctadecyl-α-*C*-D-galactopyranoside (1). A solution of **20a** (12 mg, 10 μmol) in $EtSH/BF_3{\cdot}OEt_2$ (3:1, 1.3 mL) was stirred at rt for 24 h. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH 10:1) and then was lyophilized with benzene to afford **1** (8 mg, 95%) as a white powder: ^{1}H NMR (500 MHz, C_5D_5N) δ 0.85−0.90 (m, 6H), 1.12−1.49 (m, 66H), 1.66−1.74 (m, 1H), 1.81−1.89 (m, 2H), 1.89−2.02 (m, 2H), 2.29−2.39 (m, 1H), 2.45−2.58 (m, 2H), 2.80 (dt, *J* = 8.5, 14.7 Hz, 1H), 3.08 (dt, *J* = 4.3, 14.7 Hz, 1H), 4.25−4.30 (m, 1H), 4.36−4.40 (m, 1H), 4.42−4.48 (m, 2H), 4.52−4.57 (m, 1H), 4.69 (t, *J* = 3.0 Hz, 1H), 4.71 (dd, *J* = 7.6, 11.1 Hz, 1H), 4.79 (dd, *J* = 4.8, 7.8 Hz, 1H), 5.01−5.06 (m, 1H), 5.32−5.38 (m, 1H), 8.62 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, C_5D_5N) δ 14.8, 23.4, 27.0, 27.1, 30.1, 30.27, 30.34, 30.37, 30.40, 30.42, 30.5, 30.68, 30.9, 32.6, 34.8, 37.5, 51.7, 62.4, 70.3, 71.4, 72.9, 73.3, 73.8, 76.0, 78.7, 174.0; ESI-HRMS $[M + Na^+]$ calcd for *m*/*z* $C_{50}H_{99}NNaO_8^+$ 864.7263, found 864.7271.

(2′*S*,3′*S*,4′*R*)-2′-*N*-8″-Phenyloctanoylamino-3′,4′-dihydroxyoctadecyl-α-*C*-D-galactopyranoside (1′). A solution of **20b** (5 mg, 4.9 μmol) in $EtSH/BF_3{\cdot}OEt_2$ (3:1, 1.3 mL) was stirred at rt for 24 h. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH 10:1) and then was lyophilized with benzene to afford **1′** (3 mg, 92%) as a white powder: ^{1}H NMR (500 MHz, C_5D_5N) δ 0.87 (t, *J* = 6.9 Hz, 3H), 1.15−1.53 (m, 30H), 1.65−1.74 (m, 1H), 1.77−1.85 (m, 2H), 1.89−2.01 (m, 2H), 2.31−2.39 (m, 1H), 2.42−2.55 (m, 4H), 2.80 (dt, *J* = 8.5, 14.7 Hz, 1H), 3.08 (dt, *J* = 4.5, 14.7 Hz, 1H), 4.26−4.30 (m, 1H), 4.35−4.40 (m, 1H), 4.42−4.49 (m, 2H), 4.52−4.57 (m, 1H), 4.69 (t, *J* = 3.1 Hz, 1H), 4.72 (dd, *J* = 7.6, 11.1 Hz, 1H), 4.79 (dd, *J* = 4.7, 7.8 Hz, 1H), 5.01−5.06 (m, 1H), 5.33−5.39 (m, 1H), 7.23−7.27 (m, 3H), 7.33−7.38 (m, 2H), 8.58 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, C_5D_5N) δ 14.8, 23.4, 26.9, 27.1, 29.9, 30.03, 30.08, 30.12, 30.39, 30.46, 30.49, 30.6, 30.9, 32.3, 32.6, 34.9, 36.6, 37.4, 51.7, 62.4, 70.2, 71.5, 72.9, 73.3, 73.8, 76.0, 78.7, 126.5, 129.2, 129.3, 143.7, 174.0; ESI-HRMS $[M + Na]^+$ *m*/*z* calcd for $C_{38}H_{67}NNaO_8^+$ 688.4759, found 688.4759.

(*S*,*E*)-1-(4′-Hydroxyoctadec-2′-en-5′-ynyl)-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (35a). A flame-dried 100 mL round-bottom flask was charged with commercially available ProPhenol ligand (*R*,*R*)-**34**[7] (123 mg, 0.192 mmol), 1-tetradecyne (1.12 g, 5.76 mmol), and toluene (25 mL); see Scheme S1. After the solution was degassed by two freeze−pump−thaw cycles and filled with N_2, a solution of Me_2Zn in toluene (4.8 mL, 1.2 M, 5.76 mmol) was added rapidly via syringe. The reaction mixture was stirred for 90 min at rt, and gas slowly evolved. A solution of α,β-unsaturated aldehyde **33**[1] (1.14 g, 1.92 mmol) in 10 mL of toluene, which was degassed by two freeze−pump−thaw cycles, was added via syringe over 10 s. The reaction mixture was sealed and cooled to 4 °C for 13

days without stirring. Then the reaction mixture was slowly quenched with aqueous saturated NH_4Cl solution and stirred vigorously for 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 7:2) provided a mixture of **35a** and **35b** in a ratio of 3.5:1 (1.35 g, 89% combined yield). The ratio of **35a** and **35b** and the absolute configuration of the OH-bearing carbon (C-4 position) in **35a** and **35b** were determined by analysis of the corresponding (*S*)- and (*R*)-MTPA esters.[19] Data for the major diastereoisomer **35a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.17−1.43 (m, 18H), 1.43−1.56 (m, 2H), 2.00 (br s, 1H), 2.18 (dt, J = 1.9, 7.2 Hz, 2H), 2.30−2.47 (m, 2H), 3.58 (dd, J = 4.0, 10.6 Hz, 1H), 3.70 (dd, J = 2.6, 7.0 Hz, 1H), 3.73−3.87 (m, 2H), 3.94−3.97 (m, 1H), 3.94−4.08 (m, 2H), 4.43−4.73 (m, 8H), 4.73−4.78 (m, 1H), 5.63 (dd, J = 6.3, 15.3 Hz, 1H), 5.73 (dt, J = 6.6, 15.3 Hz, 1H), 7.23−7.35 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.8, 22.6, 28.6, 28.9, 29.1, 29.3, 29.5, 29.60, 29.62, 31.9, 63.2, 72.4, 73.0, 73.2, 74.2, 76.3, 79.4, 86.7, 127.46, 127.53, 127.57, 127.73, 127.81, 127.86, 127.91, 128.25, 128.32, 129.4, 132.2, 138.2, 138.3, 138.5; ESI-HRMS $[M + Na]^+$ calcd for m/z $C_{52}H_{66}NaO_6^+$ 809.4752, found 809.4762.

(2′*R*,3′*R*,4′*S*)-1-(2′,3′-Oxiran-4′-hydroxyoctadec-5′-ynyl)-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (4) and (*R*,*E*)-1-(4′-Hydroxyoctadec-2′-en-5′-ynyl)-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (35b, Recovered). A mixture of activated 4 Å molecular sieves (2.0 g), D-(−)-DIPT (480 mg, 2.05 mmol), and CH_2Cl_2 (50 mL) was stirred at rt for 30 min. The mixture was cooled to −40 °C, and Ti(O-*i*Pr)$_4$ (486 mg, 1.71 mmol, 512 μL) was added; see Scheme S1. After the resultant mixture was allowed to stir at −40 °C for 1 h, a solution of **35a** and **35b** (ratio of 3.5:1, 1.35 g, 1.71 mmol) in CH_2Cl_2 (30 mL) was added over a 15 min period. The reaction mixture was allowed to stir at −40 °C for another 30 min, and cumene hydroperoxide (316 μL, 1.71 mmol, 80% technical grade) was added via syringe. The reaction mixture was stored at −20 °C without stirring for 3 days, and 10% aqueous D-tartaric acid solution (5 mL) was added. The reaction mixture was stirred vigorously at rt for 30 min and filtered through a plug of Celite. The filtrate was separated, and the aqueous layer was further extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were concentrated under reduced pressure. The residue was dissolved in Et_2O (50 mL), and a 5% aqueous NaOH solution (50 mL) was added. The biphasic mixture was vigorously stirred at 0 °C for 1 h. The organic phase was separated, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 3.5:1) afforded a mixture of epoxides **4** and **4′** in a ratio of 3.2:1 (1.21 g, 88% combined yield) as a colorless oil. The ratio of **4** and **4′** and the absolute configuration of the OH-bearing carbon (C-4 position) in **4** and **4′** were determined by analysis of the corresponding (*S*)- and (*R*)-MTPA esters.[19] The ^{1}H and ^{13}C NMR spectra of **4** matched the reported data:[1] ESI-HRMS $[M + Na]^+$ calcd for m/z $C_{52}H_{66}NaO_7^+$ 825.4701, found 825.4712. Data for **35b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.18−1.39 (m, 18H), 1.45−1.53 (m, 2H), 1.91 (d, J = 6.2 Hz, 1H), 2.18 (dt, J = 1.9, 7.2 Hz, 2H), 2.30−2.37 (m, 1H), 2.38−2.46 (m, 1H), 3.61 (dd, J = 4.2, 10.7 Hz, 1H), 3.69−3.77 (m, 2H), 3.80−3.88 (m, 1H), 3.95−3.99 (m, 1H), 3.99−4.07 (m, 2H), 4.45−4.72 (m, 8H), 4.75 (t, J = 5.0 Hz, 1H), 5.64 (dd, J = 6.0, 15.4 Hz, 1H), 5.78 (dt, J = 6.7, 15.4 Hz, 1H), 7.23−7.35 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.7, 22.7, 28.6, 28.9, 29.1, 29.3, 29.5, 29.6, 30.4, 31.9, 60.4, 62.9, 67.4, 70.5, 72.0, 72.5, 73.0, 73.1, 73.2, 74.2, 76.3, 79.4, 86.8, 127.48, 127.55, 127.58, 127.60, 127.78, 127.86, 127.95, 128.04, 128.27, 128.34, 129.1, 131.9, 138.2, 138.3, 138.4, 138.5.

(2′*S*,3′*S*,4′*R*)-1-(2′-Azido-3′,4′-dihydroxyoctadec-5′-ynyl)-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (5) and (4*R*,5*S*,6*S*)-6-[(2′,3′,4′,6′-Tetra-*O*-benzyl)-α-*C*-D-galactopyranoside]-3-dodecyl-5,6-dihydro-4*H*-pyrrolo[1,2-*e*][1,2,3]triazole-4,5-diol (6). NH_4Cl (203 mg, 3.8 mmol) and NaN_3 (494 mg, 7.6 mmol) were added to a mixture of epoxy alcohols **4** and **4′** (3.2:1, 320 mg, 0.38 mmol) in 9 mL of MeOH/H_2O (8/1); see Scheme S2. The reaction mixture was heated at reflux for 2 days. The reaction mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was extracted with EtOAc (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc/hexane 1:3.5) afforded **5** (202 mg, 63%): R_f 0.80 (hexane/EtOAc 1:1). The ^{1}H and ^{13}C NMR spectra matched the reported data;[1] ESI-HRMS $[M + Na]^+$ calcd for m/z $C_{52}H_{67}N_3NaO_7^+$ 868.4871, found 868.4876.

Bicyclic triazole **6** (120 mg, 35%) was obtained as a byproduct: R_f 0.25 (hexane/EtOAc 1:1); $[\alpha]_D^{24}$ +29.1 (*c* 1.6, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3H), 1.18−1.42 (m, 18H), 1.63−1.77 (m, 2H), 2.00−2.11 (m, 1H), 2.74 (dd, J = 6.4, 8.5 Hz, 2H), 2.80−2.91 (m, 2H), 3.43 (dd, J = 2.2, 10.6 Hz, 1H), 3.71−3.79 (m, 2H), 3.89−3.92 (m, 1H), 3.97−4.04 (m, 1H), 4.06−4.13 (m, 1H), 4.22 (dt, J = 11.5, 2.5 Hz, 1H), 4.43−4.73 (m, 11H), 4.82 (dd, J = 2.2, 5.2 Hz, 1H), 7.22−7.39 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.6, 27.3, 29.1, 29.34, 29.38, 29.41, 29.58, 29.63, 29.66, 31.9, 60.6, 63.7, 68.0, 72.1, 73.1, 73.2, 73.3, 73.4, 74.0, 76.2, 78.1, 127.6, 127.8, 127.87, 127.93, 128.0, 128.13, 128.18, 128.22, 128.39, 128.45, 128.52, 136.2, 137.1, 137.7, 138.0, 138.2, 143.7; ESI-HRMS $[M + Na]^+$ calcd for m/z $C_{52}H_{67}N_3NaO_7^+$ 868.4871, found 868.4883.

(*E*)-2-{[(2′,3′,4′,6′-Tetra-*O*-benzyl)-α-*C*-D-galactopyranoside]-methyl}-heptadec-2-en-4-ynal (36). Ti(O-*i*Pr)$_4$ (90 μL, 0.3 mmol) and $TMSN_3$ (79 μL, 0.6 mmol) were added to anhydrous benzene (5 mL), and the solution was heated at 80 °C under N_2 for at least 5 h; see Scheme S3. A solution of epoxides **4** and **4′** (ratio of 3.2:1, 160 mg, 0.2 mmol) in anhydrous benzene (5 mL) was added in one portion. The mixture was stirred for 30 min at 80 °C and then was cooled to rt. The solvent was removed under reduced pressure. Then Et_2O (20 mL) was added, followed by 10 mL of a 5% aqueous H_2SO_4 solution, and the solution was stirred at rt until two clear phases appeared. The mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 7:1) afforded **36** (55 mg, 35% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3H), 1.17−1.36 (m, 16H), 1.43−1.54 (m, 2H), 2.33 (dt, J = 2.1, 7.2 Hz, 2H), 2.76−2.96 (m, 2H), 3.46 (dd, J = 5.5, 8.9 Hz, 1H), 3.58 (dd, J = 7.8, 9.0 Hz, 1H), 3.77 (dd, J = 2.7, 9.5 Hz, 1H), 4.02−4.05 (m, 1H), 4.08−4.19 (m, 2H), 4.39 (d, J = 11.8 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.47−4.53 (m, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.64−4.81 (m, 4H), 4.88 (d, J = 11.6 Hz, 1H), 6.42 (t, J = 2.0 Hz, 1H), 7.20−7.41 (m, 20H), 9.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.1, 22.7, 28.4, 29.0, 29.1, 29.3, 29.5, 29.6, 31.9, 68.2, 70.8, 72.7, 72.8, 73.3, 74.4, 74.7, 76.5, 77.1, 78.5, 110.0, 127.35, 127.38, 127.47, 127.49, 127.62, 127.66, 128.0, 128.1, 128.3, 131.5, 138.3, 138.5, 138.8, 148.4, 193.95; ESI-HRMS $[M + H]^+$ calcd for m/z $C_{52}H_{65}O_6^+$ 785.4776, found 785.4784.

(2′*S*,3′*S*,4′*R*)-1-(2′-Azido-3′,4′-diacetoxyoctadec-5′-ynyl)-(2,3,4,6-tetra-*O*-benzyl)-α-*C*-D-galactopyranoside (37). To a solution of **5** (29 mg, 0.034 mmol) in anhydrous pyridine (2 mL) was added Ac_2O (0.5 mL, 5.30 mmol) at 0 °C; see Scheme S4. The reaction mixture was stirred at rt overnight. After the solvent was removed under reduced pressure, the residue was further dried under high vacuum (0.7 Torr) for 1 h, dissolved in a minimal volume of CH_2Cl_2, and filtered through a pad of silica gel in a Pasteur pipet. The pad was rinsed with 10 mL of hexane/EtOAc 3:1. Concentration of the filtrate gave diacetate **37** (21 mg, 67%) as a colorless syrup: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3H), 1.20−1.37 (m, 18H), 1.44−1.52 (m, 2H), 1.79−1.88 (m, 1H), 1.97 (s, 3H), 2.01 (s, 3H), 1.95−2.06 (m, 1H), 2.17 (dt, J = 2.0, 7.2 Hz, 2H), 3.64−3.72 (m, 3H), 3.73−3.80 (m, 1H), 3.85−3.91 (m, 1H), 3.99−4.05 (m, 2H), 4.15−4.22 (m, 1H), 4.43−4.78 (m, 8H), 5.09 (dd, J = 3.9, 7.1 Hz, 1H), 5.77 (dt, J = 2.0, 3.9 Hz, 1H), 7.23−7.36 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.7, 20.71, 20.74, 22.7, 28.4, 28.9, 29.1, 29.4, 29.5, 29.63, 29.64, 31.9, 63.7, 72.8, 73.0, 73.3, 73.6, 74.1, 76.3, 89.1, 127.5, 127.6, 127.75, 127.76, 127.9, 128.3, 128.4, 138.1, 138.2, 138.4, 138.5, 169.4, 169.7; ESI-HRMS $[M + Na]^+$ calcd for m/z $C_{56}H_{71}N_3NaO_9^+$ 952.5083, found 952.5078.

(4*R*,5*S*,6*S*)-6-[(2′,3′,4′,6′-Tetra-*O*-benzyl)-α-*C*-D-galactopyranoside]-3-dodecyl-4,5-diacetoxy-5,6-dihydro-4*H*-pyrrolo[1,2-*e*][1,2,3]triazole (21). *For the preparation of this compound from* ***6*** (Scheme S4): To a solution of **6** (17 mg, 0.020 mmol) in anhydrous pyridine (2 mL) was added 0.5 mL (5.3 mmol) of Ac_2O at 0 °C. The solution was stirred at rt overnight. After the solvent was removed under reduced pressure, the residue was further dried under high vacuum (0.7 Torr) for 1 h, dissolved in a minimal volume of CH_2Cl_2, and filtered through a pad of silica gel in a Pasteur pipet. The pad was rinsed with 10 mL of hexane/EtOAc 3:1. Concentration of the filtrate gave diacetate **21** (18 mg, 97%) as a colorless syrup. *For the preparation of compound* ***21*** *from* ***37***: A solution of **37** (10 mg, 0.011 mmol) in 2 mL of toluene was heated at reflux overnight. After the reaction was cooled to rt, removal of the solvent under reduced pressure provided **21** (10 mg, 100%) as a colorless syrup: $[\alpha]_D^{28}$ −3.0 (*c* 1.0, THF); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.20−1.36 (m, 18H), 1.54−1.69 (m, 2H), 2.01 (s, 3H), 2.03 (s, 3H), 2.24 (ddd, *J* = 2.0, 7.8, 15.1 Hz, 1H), 2.57−2.74 (m, 3H), 3.53 (dd, *J* = 4.9, 10.5 Hz, 1H), 3.64−3.67 (m, 1H), 3.70 (dd, *J* = 2.7, 7.5 Hz, 1H), 3.77−3.84 (m, 1H), 3.88−3.94 (m, 1H), 3.97 (t, *J* = 3.0 Hz, 1H), 4.04−4.10 (m, 1H), 4.36−4.75 (m, 9H), 5.81 (t, *J* = 5.6 Hz, 1H), 6.23 (d, *J* = 5.8 Hz, 1H), 7.22−7.36 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.38, 20.44, 22.7, 25.4, 29.3, 29.4, 29.56, 29.63, 29.7, 31.9, 59.9, 64.0, 67.6, 72.1, 72.9, 73.0, 73.1, 73.9, 76.1, 78.9, 127.47, 127.53, 127.55, 127.62, 127.7, 127.8, 128.0, 128.1, 128.3, 128.39, 128.42, 133.9, 137.9, 138.2, 138.3, 144.0, 169.3, 169.4; ESI-HRMS $[M + H]^+$ calcd for *m*/*z* $C_{56}H_{72}N_3O_9^+$ 930.5263, found 930.5273.

(*E*)-4-[(3′,4′,6′-Tri-*O*-benzyl)-2′-deoxy-α-*C*-D-galactopyranoside)]-2-butenal (39). A solution of alcohol **38**[32] (1.10 g, 2.25 mmol) in anhydrous CH_2Cl_2 (25 mL) at rt was treated with Dess−Martin periodinane (1.91 g, 4.50 mmol); see Scheme S5. After 1 h, TLC analysis indicated the complete consumption of the starting material. An aqueous solution of $Na_2S_2O_3$ (10%, 5 mL) was added, and the mixture was stirred until both layers became clear. The organic layer was separated and washed with saturated aqueous $NaHCO_3$ solution and water and dried (Na_2SO_4). The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 3:1) to afford aldehyde **39** (1.00 g, 91%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46−4.56 (m, 1H), 1.98−2.08 (m, 1H), 2.36−2.46 (m, 1H), 2.52−2.62 (m, 1H), 3.70 (dd, *J* = 3.7, 10.7 Hz, 1H), 3.73−3.78 (m, 1H), 3.81−3.87 (m, 1H), 3.94−4.03 (m, 1H), 4.04−4.15 (m, 2H), 4.50−4.73 (m, 6H), 6.13 (dd, *J* = 7.9, 15.7 Hz, 1H), 6.80 (dt, *J* = 7.0, 15.7 Hz, 1H), 7.24−7.37 (m, 15H), 9.46 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 33.2, 36.9, 66.3, 67.2, 71.6, 72.2, 73.2, 73.7, 75.0, 127.3, 127.5, 127.60, 127.65, 127.68, 127.8, 128.32, 128.35, 134.5, 138.2, 138.3, 138.5, 154.3, 193.8; ESI-HRMS $[M + NH_4]^+$ calcd for *m*/*z* $C_{31}H_{38}NO_5^+$ 504.2745, found 504.2746.

(*S*,*E*)-1-(4-Hydroxyoctadec-2-en-5-ynyl)-(3,4,6-tri-*O*-benzyl)-2-deoxy-α-*C*-D-galactopyranoside (40a). A flame-dried 100 mL round-bottom flask was charged with commercially available ProPhenol ligand (*R*,*R*)-**34**[7] (76 mg, 0.12 mmol), 1-tetradecyne (682 mg, 3.51 mmol), and toluene (15 mL); see Scheme S5. A solution of Me_2Zn in toluene (2.9 mL, 1.2 M, 3.51 mmol) was added rapidly via syringe. The reaction mixture was stirred for 90 min at rt, and gas slowly evolved. A solution of α,β-unsaturated aldehyde **39** (0.57 g, 1.17 mmol) in 5 mL of toluene was added via syringe over 10 s. The reaction mixture was sealed and cooled to 4 °C for 13 days without stirring. Then the reaction was slowly quenched with aqueous saturated NH_4Cl solution, with vigorous stirring for 15 min. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 3:1) provided a mixture of **40a** and **40b** in a ratio of 3:2 (327 mg, 41% combined yield). The ratio of **40a** and **40b** and the absolute configuration of the OH-bearing carbon (C-4 position) in **40a** and **40b** were determined by analysis of the corresponding (*S*)- and (*R*)-MTPA esters.[19] Data for the major diastereoisomer **40a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.16−1.39 (m, 17H), 1.43−1.59 (m, 3H), 1.72 (s, 1H), 1.98−2.11 (m, 2H), 2.13−2.24 (m, 3H), 2.30−2.41 (m, 1H), 3.61−3.70 (m, 1H), 3.72−3.76 (m, 1H), 3.77−3.83 (m, 1H), 3.84−3.94 (m, 1H), 3.96−4.07 (m, 2H), 4.46−4.75 (m, 6H), 4.76−4.82 (m, 1H), 5.62 (dd, *J* = 6.3, 15.3 Hz, 1H), 5.73−5.86 (m, 1H), 7.21−7.38 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.8, 22.7, 28.6, 28.9, 29.1, 29.3, 29.5, 29.61, 29.63, 31.9, 35.8, 63.1, 68.0, 71.2, 72.5, 73.2, 73.5, 74.8, 79.4, 86.8, 127.30, 127.47, 127.55, 127.79, 127.84, 128.26, 128.32, 128.34, 129.0, 132.3, 138.3, 138.4, 138.6; ESI-HRMS $[M + Na]^+$ calcd for *m*/*z* $C_{45}H_{60}NaO_5^+$ 703.4333, found 703.4338.

(2′*R*,3′*R*,4′*S*)-1-(2′,3′-Oxiran-4′-hydroxyoctadec-5′-ynyl)-(3,4,6-tri-*O*-benzyl)-2-deoxy-α-*C*-D-galactopyranoside (26). A mixture of activated 4 Å molecular sieves (0.15 g), D-(−)-DIPT (28.5 mg, 0.122 mmol), and CH_2Cl_2 (10 mL) was stirred at rt for 30 min; see Scheme S5. After the mixture was cooled to −40 °C, Ti(O-*i*Pr)$_4$ (29 mg, 0.101 mmol, 30 μL) was added. The resultant mixture was allowed to stir at −40 °C for 1 h, and a solution of **40a** and **40b** (3:2, 115 mg, 0.169 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The reaction mixture was allowed to stir at −40 °C for another 30 min, and cumene hydroperoxide (19 μL, 0.10 mmol, 80% technical grade) was added via syringe. The reaction mixture was stored at −20 °C without stirring for 3 days, and 10% aqueous D-tartaric acid solution (1 mL) was added. The reaction mixture was stirred vigorously at rt for 30 min and filtered through a plug of Celite. The aqueous layer of the filtrate was further extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were concentrated under reduced pressure. The residue was dissolved in Et_2O (20 mL), and 5% aqueous NaOH solution (20 mL) was added. The biphasic mixture was stirred vigorously at 0 °C for 1 h. The organic phase was separated, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 4:1 to 3:1) afforded a mixture of epoxides **26** and **26′** in a ratio of 3.4:1 (38 mg, 32% combined yield) as a colorless oil. The ratio of **26** and **26′** and the absolute configurations of the OH-bearing carbons (C-4 position) in **26** and **26′** were determined by analysis of the corresponding (*S*)- and (*R*)-MTPA esters.[19] Data for the major diastereoisomer **26**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.20−1.39 (m, 17H), 1.45−1.52 (m, 2H), 1.52−1.58 (m, 1H), 1.64 (s, 1H), 1.66−1.72 (m, 2H), 2.03−2.10 (m, 1H), 2.19 (dt, *J* = 1.9, 7.2 Hz, 2H), 2.84−2.87 (m, 1H), 2.92−2.95 (m, 1H), 2.99 (dt, *J* = 2.0, 5.9 Hz, 1H), 3.56−3.62 (m, 1H), 3.68−3.71 (m, 1H), 3.78−3.83 (m, 1H), 3.99−4.08 (m, 2H), 4.08−4.14 (m, 1H), 4.18−4.22 (m, 1H), 4.51−4.69 (m, 6H), 7.24−7.36 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.7, 22.7, 28.5, 28.9, 29.1, 29.3, 29.5, 29.61, 29.64, 31.9, 55.2, 60.4, 62.6, 67.3, 71.5, 72.1, 73.21, 73.28, 73.30, 75.0, 87.2, 127.3, 127.5, 127.63, 127.70, 127.75, 128.1, 128.31, 128.33, 128.38, 137.9, 138.2, 138.5; ESI-HRMS $[M + NH_4]^+$ calcd for *m*/*z* $C_{45}H_{64}NO_6^+$ 714.4728, found 714.4729.

(4*R*,5*S*,6*S*)-6-[(3′,4′,6′-Tri-*O*-benzyl)-2′-deoxy-α-*C*-D-galactopyranoside]-3-dodecyl-5,6-dihydro-4*H*-pyrrolo[1,2-*e*][1,2,3]-triazole-4,5-diol (41). NH_4Cl (12 mg, 0.22 mmol) and NaN_3 (28 mg, 0.43 mmol) were added to epoxy alcohols **26** and **26′** (3.4:1, 15 mg, 0.022 mmol) in 2.25 mL of MeOH/H_2O (2/0.25); see Scheme S5. The reaction mixture was heated at reflux for 2 days. The reaction mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was extracted with EtOAc (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide a residue that was dissolved in 5 mL of toluene. The solution was heated at reflux overnight, and the solvent was removed under reduced pressure. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 1:1) provided bicyclic triazole **41** along with an inseparable byproduct (13 mg, 82%, two steps). Data for **41**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.19−1.39 (m, 20H), 1.57−1.74 (m, 4H), 1.79−1.86 (m, 1H), 2.07−2.14 (m, 1H), 2.70−2.76 (m, 2H), 2.92 (s, 1H), 3.56 (dd, *J* = 2.4, 10.9 Hz, 1H), 3.73 (dd, *J* = 2.9, 4.4 Hz, 1H), 3.90−3.95 (m, 1H), 4.14−4.19 (m, 1H), 4.21−4.28 (m, 1H), 4.45−4.72 (m, 8H), 4.83−4.88 (m, 1H), 7.24−7.39 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.6, 29.1, 29.36, 29.38, 29.42, 29.59, 29.64, 29.66, 31.9, 71.9, 72.2, 72.89, 72.94, 73.3, 75.0, 78.2, 127.5, 127.7, 127.8, 127.9, 128.1, 128.3, 128.46, 128.51,

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136.3, 137.2, 138.0, 138.3, 143.8; ESI-HRMS $[M + Na]^+$ calcd for m/z $C_{45}H_{61}N_3NaO_6^+$ 762.4453, found 762.4463.

(4*R*,5*S*,6*S*)-6-[(3′,4′,6′-Tri-*O*-benzyl)-2′-deoxy-α-*C*-D-galacto-pyranoside]-3-dodecyl-4,5-diacetoxy-5,6-dihydro-4*H*-pyrrolo-[1,2-*e*][1,2,3]triazole (27). To a solution of **41** (5 mg, 6.7 μmol) in anhydrous pyridine (1 mL) was added 0.25 mL (2.7 mmol) of Ac_2O at 0 °C; see Scheme S5. The solution was stirred at rt overnight. After the solvent was removed under reduced pressure, the residue was further dried under high vacuum (0.7 Torr) for 1 h, dissolved in a minimal volume of CH_2Cl_2, and filtered through a pad of silica gel in a Pasteur pipet. The pad was rinsed with 10 mL of hexane/EtOAc 3:1. Concentration of the filtrate gave diacetate **27** (5 mg, 91%) as a colorless syrup: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.19−1.35 (m, 18H), 1.50−1.66 (m, 2H), 1.96−2.15 (m, 8H), 2.56−2.72 (m, 4H), 3.59−3.65 (m, 1H), 3.74−3.84 (m, 3H), 3.86−3.93 (m, 1H), 4.08−4.14 (m, 1H), 4.39−4.74 (m, 7H), 5.83 (t, J = 5.5 Hz, 1H), 6.27 (d, J = 5.8 Hz, 1H), 7.24−7.35 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 20.4, 20.5, 22.7, 25.4, 29.34, 29.35, 29.39, 29.57, 29.64, 29.65, 29.67, 31.9, 60.1, 64.2, 68.0, 71.2, 72.96, 73.00, 79.0, 127.39, 127.43, 127.5, 127.6, 127.7, 127.9, 128.29, 128.32, 128.4, 134.0, 138.26, 138.33, 138.37, 169.49, 169.53; ESI-HRMS $[M + H]^+$ calcd for m/z $C_{49}H_{66}N_3O_8^+$ 824.4844, found 824.4840.

(*S*,*E*)-1-(4′-Methoxybenzyloxy)henicos-5-en-2-yn-4-ol (44a). A flame-dried round-bottom flask was charged with commercially available ProPhenol ligand (*R*,*R*)-**34**[7] (360 mg, 0.563 mmol), alkyne **43** (2.98 g, 16.9 mmol), and 150 mL of toluene; see Scheme S6. A solution of Me_2Zn in toluene (14.1 mL, 1.2 M, 16.9 mmol) was added rapidly via syringe. The reaction mixture was stirred for 90 min at rt, and gas slowly evolved. A solution of α,β-unsaturated aldehyde **42** (1.50 g, 5.63 mmol) in a minimal volume of toluene was added via syringe over 10 s. The reaction mixture was sealed and cooled to 4 °C for 4 days without stirring. Then the reaction was slowly quenched with aqueous saturated NH_4Cl solution, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 200 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 7:2) provided a mixture of **44a** and **44b** in a ratio of 3.2:1 (2.15 g, 86% combined yield). The ratio of **44a** and **44b** and the absolute configurations of OH-bearing carbons (C-4 position) in **44a** and **44b** were determined by analysis of its corresponding (*S*)- and (*R*)-MTPA esters.[19] Data for **44a**/**44b** (ratio = 3.2:1): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.19−1.43 (m, 26H), 2.01−2.09 (m, 2H), 2.54 (s, 1H), 3.78 (s, 3H), 4.18 (d, J = 1.6 Hz, 2H), 4.52 (s, 2H), 4.84−4.90 (m, 1H), 5.59 (dd, J = 6.1, 15.3 Hz, 1H), 5.87 (dt, J = 6.7, 15.3 Hz, 1H), 6.84−6.89 (m, 2H), 7.24−7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 28.8, 29.1, 29.3, 29.4, 29.51, 29.55, 29.59, 31.82, 31.86, 55.1, 56.9, 62.8, 71.1, 81.6, 86.1, 113.7, 128.7, 129.3, 129.7, 133.9, 159.3; ESI-HRMS $[M + NH_4]^+$ calcd for m/z $C_{29}H_{50}NO_3^+$ 460.3785, found 460.3785.

(*R*)-4-(4″-Methoxybenzyloxy)-1-((2′*R*,3′*R*)-3′-pentadecyloxiran-2′-yl)but-2-yn-1-ol (22). Four Å molecular sieves (the amount is not critical if the allyl propargyl alcohol, CH_2Cl_2, and cumene hydroperoxide are predried) were added to a solution of D-(−)-DIPT (881 mg, 3.76 mmol) in 30 mL of dry CH_2Cl_2; see Scheme S6. The mixture was stirred at rt for 30 min before it was cooled to −40 °C. $Ti(O\text{-}iPr)_4$ (890 mg, 3.13 mmol) was added to the reaction mixture, which was stirred for 30 min. After cumene hydroperoxide (578 μL, 3.13 mmol, 80% technical grade) was added, the reaction mixture was stirred for 30 min. A solution of **44a**/**44b** (ratio of 3.2:1, 1.80 g, 4.07 mmol) in a minimal volume of dry CH_2Cl_2 was added dropwise, and the reaction mixture was sealed and stored at −20 °C without stirring for 3 days. An aqueous precooled (0 °C) solution of tartaric acid (2 mL, 10% w/v) was added dropwise, and the reaction mixture was stirred vigorously at rt for 30 min and filtered through a pressed pad of Celite. The organic layer was separated, washed with brine, and concentrated. The residue was dissolved in Et_2O (10 mL) at 0 °C, and the solution was treated with a solution (1 mL) of 30% w/v NaOH in saturated brine. The two-phase mixture was stirred vigorously for 1 h at 0 °C. The phases were separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 3:1) to afford **22** (1.05 g, 56%, maximum yield 77%, dr >20:1). The dr value and the absolute configurations of OH-bearing carbons (C-4 position) in **22** were determined by analysis of its corresponding (*S*)- and (*R*)-MTPA esters.[19] Data for **22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.20−1.51 (m, 26H), 1.56−1.62 (m, 2H), 2.13−2.19 (m, 1H), 3.02 (dd, J = 2.5, 3.1 Hz, 1H), 3.11 (dt, J = 2.2, 5.7 Hz, 1H), 3.81 (s, 3H), 4.19 (d, J = 1.6 Hz, 2H), 4.52 (s, 2H), 4.62−4.66 (m, 1H), 6.86−6.90 (m, 2H), 7.26−7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.9, 29.33, 29.35, 29.52, 29.55, 29.64, 29.68, 31.2, 31.9, 55.3, 56.1, 56.9, 59.5, 61.0, 71.3, 82.7, 82.9, 113.8, 129.2, 129.8, 159.4; ESI-HRMS $[M + Na]^+$ calcd for m/z $C_{29}H_{46}NaO_4^+$ 481.3288, found 481.3287.

(4*R*,5*S*,6*S*)-3-((4′-Methoxybenzyloxy)methyl)-5,6-dihydro-6-pentadecyl-4*H*-pyrrolo[1,2-*e*][1,2,3]-triazole-4,5-diol (46). To epoxy alcohol **22** (1.0 g, 2.18 mmol) in 27 mL of $MeOCH_2CH_2OH/H_2O$ (8:1) were added NH_4Cl (1.17 g, 21.8 mmol) and NaN_3 (2.83 g, 43.6 mmol); see Scheme S6. The reaction mixture was heated at reflux for 48 h. The reaction mixture was allowed to cool to rt, and the solvents were evaporated. The residue was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (EtOAc/hexane 1:1) afforded **46** (951 mg, 87%, two steps): $[\alpha]_D^{26}$ +3.7 (*c* 1.7, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.20−1.40 (m, 24H), 1.43−1.53 (m, 1H), 1.55−1.66 (m, 1H), 1.78−1.87 (m, 1H), 1.90−1.99 (m, 1H), 3.42−3.47 (m, 1H), 3.81 (s, 3H), 3.81 (m, 1H), 4.42 (dt, J = 3.2, 6.8 Hz, 1H), 4.53 (dd, J = 5.0, 8.3 Hz, 1H), 4.59 (s, 2H), 4.76 (s, 2H), 5.08−5.11 (m, 1H), 6.88−6.92 (m, 2H), 7.27−7.31 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 29.36, 29.38, 29.56, 29.63, 29.68, 29.71, 31.9, 32.2, 55.3, 63.9, 64.8, 66.6, 73.2, 80.7, 114.1, 129.0, 129.8, 138.3, 140.3, 159.7; ESI-HRMS $[M + H]^+$ calcd for m/z $C_{29}H_{48}N_3O_4^+$ 502.3639, found 502.3651.

(4*R*,5*S*,6*S*)-3-((4′-Methoxybenzyloxy)methyl)-4,5-diacetoxy-5,6-dihydro-6-pentadecyl-4*H*-pyrrolo-[1,2-*e*][1,2,3]triazole (23). To a solution of 20 mg (40 μmol) of **46** in 1 mL of CH_2Cl_2 were added Et_3N (100 μL, 717 μmol) and Ac_2O (50 μL, 530 μmol); see Scheme S6. The solution was stirred overnight at rt. After the solvent was removed, the residue was further dried under high vacuum (0.7 Torr) for 1 h, dissolved in a minimal volume of CH_2Cl_2, and filtered through a pad of silica gel in a Pasteur pipet. The pad was rinsed with 10 mL of hexane/EtOAc 4:1. Concentration gave diacetate **23** (24 mg, 99%) as a colorless syrup: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.20−1.48 (m, 25H), 1.60−1.70 (m, 1H), 1.86−1.96 (m, 1H), 1.99 (s, 3H), 2.06−2.16 (m, 1H), 2.12 (s, 3H), 3.80 (s, 3H), 4.52 (s, 2H), 4.57 (q, J = 6.2 Hz, 1H), 4.65 (s, 2H), 5.54 (t, J = 5.8 Hz, 1H), 6.20 (d, J = 5.6 Hz, 1H), 6.84−6.88 (m, 2H), 7.24−7.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.3, 20.4, 22.6, 25.0, 29.21, 29.24, 29.29, 29.4, 29.52, 29.56, 29.58, 29.62, 31.6, 31.8, 55.2, 62.0, 63.0, 63.7, 72.3, 78.3, 113.7, 129.5, 129.9, 134.9, 140.6, 159.2, 169.2, 169.4; ESI-HRMS $[M + H]^+$ calcd for m/z $C_{33}H_{52}N_3O_6^+$ 586.3851, found 586.3848.

(4*R*,5*S*,6*S*)-5,6-Dihydro-3-(hydroxymethyl)-6-pentadecyl-4*H*-pyrrolo[1,2-*e*][1,2,3]triazole-4,5-diol (47). To a solution of **46** (770 mg, 1.53 mmol) in CH_2Cl_2/H_2O (10 mL, 20:1) was added DDQ (3.48 mg, 15.3 mmol) at rt under N_2; see Scheme S6. The reaction was stirred at rt for 3 h and diluted with CH_2Cl_2. The solution was extracted with saturated aqueous $NaHCO_3$ solution, dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel ($CHCl_3$/MeOH 20:1) to provide triol **47** (584 mg, 91%) as a white solid: $[\alpha]_D^{25}$ −4.2 (*c* 0.52, THF); ^{1}H NMR (500 MHz, $CD_3OD/CDCl_3$ 1:1) δ 0.88 (t, J = 6.9 Hz, 3H), 1.20−1.46 (m, 24H), 1.51−1.61 (m, 1H), 1.67−1.76 (m, 1H), 1.89−1.98 (m, 1H), 2.02−2.11 (m, 1H), 4.36 (q, J = 6.0 Hz, 1H), 4.42 (t, J = 5.5 Hz, 1H), 4.75 (d, J = 4.8 Hz, 2H), 5.07 (d, J = 5.3 Hz, 1H); ^{13}C NMR (125 MHz, $CD_3OD/CDCl_3$ 1:1) δ 13.1, 22.0, 24.7, 28.7, 28.8, 28.9, 29.0, 31.0, 31.3, 54.6, 63.3, 64.0, 79.8, 138.1, 141.4; ESI-HRMS $[M + H]^+$ calcd for m/z $C_{21}H_{40}N_3O_3^+$ 382.30697, found 382.30675.

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(4*R*,5*S*,6*S*)-4,5-Dibenzoyloxy-5,6-dihydro-3-(benzoyloxy)-methyl)-6-pentadecyl-4*H*-pyrrolo[1,2-*e*][1,2,3]triazole (32). To a solution of **47** (10 mg, 0.026 mmol) in 2 mL of THF were added iPr$_2$NEt (68 μL, 0.393 mmol), benzoyl chloride (27.4 μL, 0.236 mmol), and DMAP (1 mg, 8.2 μmol) at rt; see Scheme S6. The solution was stirred overnight at rt. After the solvent was removed, the residue was further dried under high vacuum (0.7 Torr) for 1 h, dissolved in a minimal volume of CH_2Cl_2, and filtered through a pad of silica gel in a Pasteur pipet. The pad was rinsed with 5 mL of hexane/EtOAc 3:1. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 15:1) gave **32** (18 mg, 99%) as a slightly yellow solid: $[\alpha]_D^{27}$ −16.0 (*c* 0.3, THF); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.0 Hz, 3H), 1.17−1.34 (m, 22H), 1.35−1.45 (m, 2H), 1.46−1.56 (m, 1H), 1.68−1.79 (m, 1H), 2.03−2.13 (m, 1H), 2.23−2.33 (m, 1H), 4.85 (q, J = 6.1 Hz, 1H), 5.54 (d, J = 12.8 Hz, 1H), 5.61 (d, J = 12.8 Hz, 1H), 6.00 (t, J = 5.8 Hz, 1H), 6.61 (d, J = 5.7 Hz, 1H), 7.21−7.27 (m, 4H), 7.31−7.35 (m, 1H), 7.43 (tt, J = 7.5, 1.2 Hz, 1H), 7.47 (tt, J = 7.5, 1.2 Hz, 1H), 7.54 (tt, J = 7.5, 1.2 Hz, 1H), 7.73−7.77 (m, 2H), 7.87−7.94 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.0, 29.3, 29.5, 29.6, 29.7, 31.8, 31.9, 57.7, 62.9, 64.7, 78.8, 128.2, 128.3, 128.4, 128.5, 129.5, 129.7, 129.8, 132.9, 133.4, 133.8, 135.9, 138.7, 164.9, 165.1, 166.1; ESI-HRMS $[M + H]^+$ calcd for m/z $C_{42}H_{52}N_3O_6^+$ 694.3851, found 694.3850.

(*R*)-4-(4″-Methoxybenzyloxy)-1-((2′*S*,3′*S*)-3′-pentadecyloxiran-2′-yl)but-2-yn-1-ol (28). Four Å molecular sieves (the amount is not critical if the allyl propargyl alcohol, CH_2Cl_2, and cumene hydroperoxide are predried) were added to a solution of L-(+)-DIPT (81 mg, 0.35 mmol) in 5 mL of dry CH_2Cl_2; see Scheme S7. The mixture was stirred at rt for 30 min before it was cooled to −40 °C. Ti(O-iPr)$_4$ (86 μL, 0.29 mmol) was added to the reaction mixture, which was stirred for 30 min. After cumene hydroperoxide (54 μL, 0.29 mmol, 80% technical grade) was added, the reaction mixture was stirred for 30 min. A solution of **44a**/**44b** (ratio of 7:1, 128 mg, 0.29 mmol) in a minimal volume of dry CH_2Cl_2 was added dropwise, and the reaction mixture was sealed and stored at −20 °C without stirring for 3 days. After an aqueous precooled (0 °C) solution of tartaric acid (1 mL, 10% w/v) was added dropwise, the reaction mixture was stirred vigorously at rt for 30 min and filtered through a pressed pad of Celite. The organic layer was separated, washed with brine, and concentrated. The residue was dissolved in Et_2O (5 mL) at 0 °C, and the solution was treated with a solution (1 mL) of 30% w/v NaOH in saturated brine. The two-phase mixture was stirred vigorously for 1 h at 0 °C. The phases were separated, the aqueous layer was extracted with Et_2O, and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/EtOAc 5:1) to afford a mixture of **28** and **22** in a ratio of 3.7:1 (55 mg, 61% combined yield). The ratio of **28** and **22** and the absolute configurations of the OH-bearing carbons (C-4 position) in **28** and **22** were determined by analysis of its corresponding (*S*)- and (*R*)-MTPA esters.[19] Data for the major diastereoisomer **28**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.15−1.49 (m, 26H), 1.51−1.61 (m, 2H), 2.53−2.70 (m, 1H), 2.97−3.02 (m, 2H), 3.79 (s, 3H), 4.17 (d, J = 1.4 Hz, 2H), 4.32−4.37 (m, 1H), 4.51 (s, 2H), 6.84−6.89 (m, 2H), 7.24−7.29 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.8, 29.29, 29.31, 29.47, 29.51, 29.60, 29.62, 29.64, 31.2, 31.9, 55.2, 56.5, 56.8, 60.4, 62.2, 71.3, 82.0, 83.6, 113.8, 129.2, 129.7, 159.3.

(4*R*,5*R*,6*R*)-3-((4-Methoxybenzyloxy)methyl)-4,5-diacetoxy-5,6-dihydro-6-pentadecyl-4*H*-pyrrolo-[1,2-*e*][1,2,3]triazole (29). To epoxy alcohol **28**/**22** (3.7:1, 42 mg, 0.092 mmol) in 4.5 mL of $MeOCH_2CH_2OH/H_2O$ (8:1) were added NH_4Cl (49 g, 0.92 mmol) and NaN_3 (119 g, 1.83 mmol); see Scheme S7. The reaction mixture was heated at reflux for 48 h. The reaction mixture was allowed to cool to rt, and the solvents were evaporated. The residue was extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to provide a residue. To a solution of the residue in 1 mL of CH_2Cl_2 were added 108 μL (0.78 mmol) of Et_3N and 49 μL (0.518 mmol) of Ac_2O. The solution was stirred overnight at rt. After the solvent was removed, the residue was further dried under high vacuum (0.7 Torr) for 1 h, dissolved in a minimal volume of CH_2Cl_2, and filtered through a pad of silica gel in a buret. The pad was rinsed with 5 mL of hexane/EtOAc 4:1. The filtrate was concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel (hexane/EtOAc 3:1) gave a mixture of **29** and **23** in a ratio of 2.7:1 (41 mg, 76% combined yield) as a colorless syrup. Data for the major diastereoisomer **29**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 6.9 Hz, 3H), 1.20−1.48 (m, 26H), 1.60−1.70 (m, 1H), 1.97−2.06 (m, 1H), 2.01 (s, 3H), 2.11 (s, 3H), 3.80 (s, 3H), 4.43 (dt, J = 1.9, 6.9 Hz, 1H), 4.51 (s, 2H), 4.63 (s, 2H), 5.51 (t, J = 1.7 Hz, 1H), 5.98 (d, J = 1.4 Hz, 1H), 6.84−6.88 (m, 2H), 7.24−7.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.5, 20.7, 22.7, 25.4, 29.1, 29.29, 29.32, 29.5, 29.56, 29.61, 29.65, 31.9, 33.2, 55.2, 62.9, 65.4, 69.1, 72.3, 85.6, 113.7, 127.5, 127.8, 128.0, 129.6, 135.9, 169.4, 169.6.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Schemes S1−S7, copies of 2D NOESY spectra of **25** and **32** using different mixing times, and copies of ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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