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Synthesis of phytosphingosine using olefin cross-metathesis: a convenient access to chain-modified phytosphingosines from D-lyxose

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Abstract—This work establishes a general protocol for synthesizing phytosphingosines with various lengths of lipid chains. The synthetic strategy included the Wittig reaction and olefin cross-metathesis as key steps. Combining these two C–C bond formation methods provide rapid access to adequately protected phytosphingosine backbones.

1. Introduction

Sphingolipids are highly diverse bioactive compounds as both first and second messengers[1] and backbones of glycosphingolipids.[2] Glycosphingolipids contain two basic structural motifs—carbohydrate (hydrophilic head) and ceramide (lipophilic tail). The ceramide portion comprises sphingoid bases (glycosyl acceptors), which are long-chain alkanes or alkenes of around 14–20 carbons in length with an amide-linked fatty acyl chain at position 2 and hydroxyl substituents at positions 1 and 3, as presented in Figure 1 for phytosphingosine **1**.

Phytosphingosines and their glycosylated derivatives[3] are biologically important and have attracted many attentions. New methods for synthesizing them have been developed.[4] Most methods for synthesizing phytosphingosines involve carbohydrates[5] and amino acids[5a] as chiral starting materials; asymmetric syntheses are fewer.[6] Recently, given the availability of powerful ruthenium-based olefin cross-metathesis (CM) reagents,[7] sphingolipid and glycolipids were synthesized by the CM of two terminal olefins.[8] As part of our program to develop glycolipid-based vaccines and adjuvants, we have developed the synthesis of glycosphingolipids, and evaluated their cell proliferation activities of mouse splenocytes as well as the expression of cytokines IFN-γ and IL-4.[4a] Modifications of the lipid chain length in α-galactosyl ceramides can influence an array of cytokines' release and demonstrate a profound relationship between structure and activity.[3b,4c] In this publication, we report an efficient route for construction of a small phytosphingosine library (**2** in Fig. 1) based on the modification of lipid chain from commercially available D-lyxose, with CM as a key step.

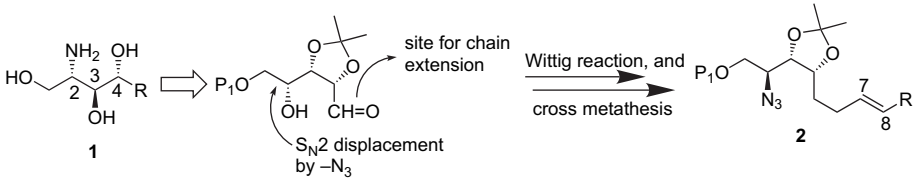

Figure 1. Retrosynthesis and steps involved in the synthesis of phytosphingosine analog **2** from D-lyxose.

Keywords: Phytosphingosine; Cross-metathesis; Wittig reaction; Lipid.
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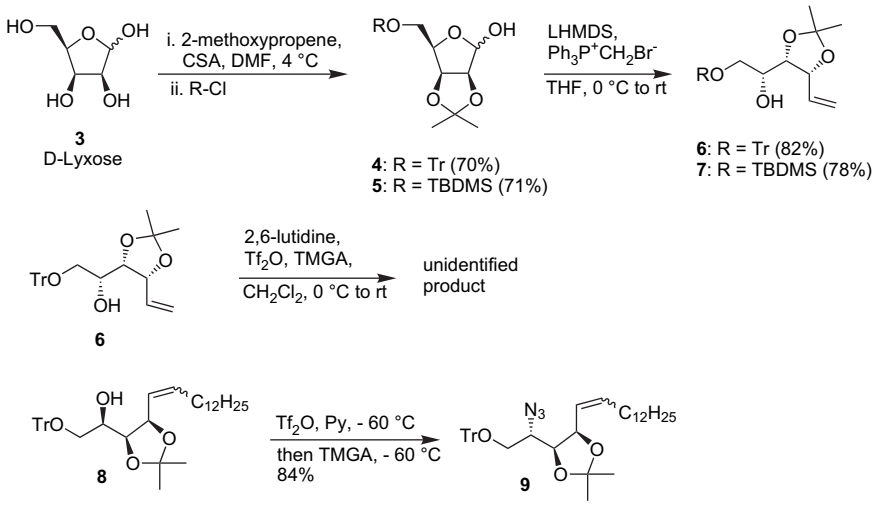
Following in this vein, we demonstrated the advantage of using D-lyxose as an excellent five-carbon building block to generate the desired core structure, 2-amino-1,3,4-triol moiety,[5b] with an appropriate stereochemical disposition, corresponding to the phytosphingosine, while providing a chemical handle for further synthesis. The lipid chains of phytosphingosine analogs were extended by the Wittig reaction with various ylides. However, such an approach for synthesizing a phytosphingosine library is not straightforward because various Wittig reagents must be prepared in each case. In the present study, we employed Wittig reaction to construct the core building block and elaborated CM reaction to produce the lipid library, as presented in Figure 1.

2. Results and discussion

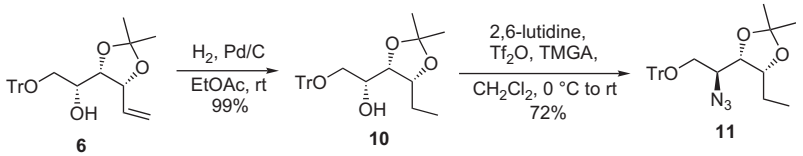
In this context, the sequential application of the Wittig reaction and olefin cross-metathesis to the syntheses of phytosphingosine analogs **2** was investigated. In Scheme 1, the core compounds **6**–**7** were synthesized from D-lyxose **3**. In brief, selective acetal formation at the 2,3-dihydroxyl groups of **3** using 2-methoxypropene was followed by tritylation (TrCl, Py, 50 °C)[9] or silylation (TBDMSCl, imidazole, DMF, 0 °C) of the primary hydroxyl group to yield **4**[5b] and **5** (70% over two steps). Wittig reaction of the acetals **4** and **5** with phosphonium salt $Ph_3P^+CH_3Br^-$ in the presence of lithium hexamethyldisilazide (LHMDS) at 0 °C produced hydroxy-alkenes **6** and **7** in 82% and 78% yield, respectively.[5a] Attempt to introduce an azide group by triflate activation of the free hydroxyl group and substitution by azide using tetramethylguanidium azide (TMGA) at this stage in **6** gave an unidentified compound. Although we got correct molecular ion (MW 456.2287) and IR absorption of azide (2106 cm^{-1}) of the compound as the desired product, but one proton was missed according to the ^1H NMR spectrum. Notably, when the reaction temperature was lowered to −60 °C, only triflate product was observed. These results are unexpected, since in our earlier work,[5b] we observed that alcohol **8** underwent smooth azidation to **9** by triflate activation followed by treatment with TMGA in the presence of internal olefin. The difficulty over the course of this azidation reaction in **6** is still unknown to us.

We envisioned that perhaps the terminal double bond in **6** prohibited azidation during S_N2 type reaction, and an azido replacement could be achieved onto fully hydrogenated alcohol **10** (Scheme 2). Thus, the double bond in **6** was reduced to **10**, which was treated with trifluoromethanesulfonic anhydride (Tf_2O) followed by TMGA to afford the azide **11** in 72% yield with inversion of configuration.

An earlier report on intramolecular alkene–azide cyclization,[10] the above results and the need for terminal olefin as a cross-metathesis component motivated us to insert two more carbons for extending the distance between reaction carbon center and terminal olefin. Hopefully, this chain extension will block the unknown reaction that occurred during our initial azido replacement studies. Therefore, a detailed study was conducted to prepare α,β-unsaturated esters **12** and **13**. Motivated by the recent development of the Wittig reaction on sugar lactols,[11] reactions of **4** with stabilized ylide under various conditions were investigated, as shown in Table 1.

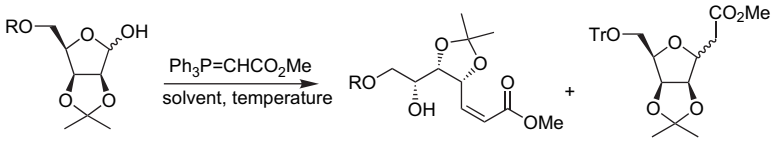


Scheme 1. Azido replacement studies.



Scheme 2. Azide substitution reaction onto saturated alcohol **10**.

Table 1. Effect of solvent and temperature on the Wittig reaction of **4** and **5**



4: R = Tr
5: R = TBDMS

***Z*-12**: R = Tr
***Z*-13**: R = TBDMS

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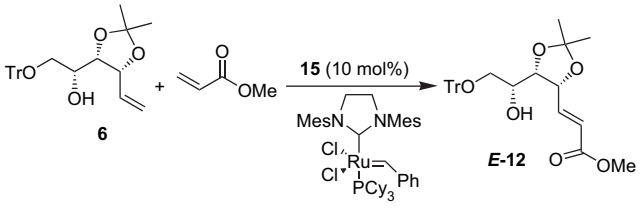
Entry	Substrate	Solvent	Temperature (°C)	Additives	Products	Yields (%)
1	**4**	CH_3CN	40	—	**14**	70
2	**4**	CH_3CN	80	—	**14**	50
3	**4**	Toluene	90	—	**14**	50
4	**4**	CH_2Cl_2	rt	—	*Z*-**12**	35
5	**4**	CH_2Cl_2	40	Benzoic acid	—	—
6	**4**	Toluene	90	Benzoic acid	—	—
7	**4**	CH_3CN	40	Benzoic acid	—	—
8	**5**	CH_3CN	rt	—	*Z*-**13**	30
9	**5**	Toluene	rt	—	*Z*-**13**	20
10	**5**	CH_2Cl_2	rt	—	*Z*-**13**	40
11	**5**	CH_3CN	70	—	*Z*-**13**	30
12	**5**	CH_2Cl_2	50	—	*Z*-**13**	40

An initial attempt to react $(EtO)_2P(O)CH_2CO_2Et$ with **4** using DBU, NaH, and LHMDS as bases, respectively, in various solvents (such as CH_3CN, THF, and DMSO), while using LiCl as a promoter, failed to give **12** in an acceptable yield. Reaction of **4** with stabilized ylide ($Ph_3P{=}CHCO_2Me$) in acetonitrile at 40 °C gave the undesired Michael adduct **14** as a mixture of α- and β-*C*-glycosides (entry 1).[11a] An increase in temperature (entry 2) and change in solvent (entry 3) had little effect on the product yield. To our surprise, this Wittig reaction in the presence of benzoic acid in refluxing dichloromethane[12] (entry 5), toluene (entry 6), and acetonitrile (entry 7), respectively, did not led to product formation. We then examined TBDMS ether protected lactol **5** for the Wittig reaction, and similar results were obtained as expected. Compound **5** reacted with the ylide in acetonitrile (entry 8) or toluene (entry 9) at room temperature to provide *Z*-**13** in 30% and 20% yield, respectively, while the same Wittig reaction performed in THF, DMF or 1,2-dichloroethane resulted no product formation. Furthermore, the yield was not significantly improved by increasing reaction temperature (entries 11 and 12). After extensive experimentations, it was found that the Wittig olefination of **4** and **5** with stabilized ylide ($Ph_3P{=}CHCO_2Me$) was best performed at room temperature in dichloromethane (entries 4 and 10) with the isolated yield of 35% and 40% for *Z*-**12** and *Z*-**13**, respectively. The cis stereochemistries of the products were determined by ^1H NMR analysis as the coupling constant of the two olefinic protons is 11.6 Hz.

Alternatively, **12** can also be obtained by the cross-metathesis of alkene **6** with methyl acrylate. Table 2 presents details of the use of Grubbs' second-generation catalyst **15**[13] for hetero-CM reaction. Under the reaction conditions used for CM (10.0 mol % catalyst **15**, CH_2Cl_2, rt), the reaction of alkene **6** in the presence of 2.0 equiv of methyl acrylate led to the formation of the desired CM product *E*-**12** in 20% yield (entry 1). The addition of 20.0 (entry 2) and 10.0 equiv (entry 4) of methyl acrylate at refluxing temperature led to an increased yield of 31% and 37%, respectively. Use of additives and changing solvents and reaction temperature were not beneficial (entries 5 and 6). However, when toluene was used as solvent in the presence of 0.3 equiv of $Ti(O^iPr)_4$ at 75 °C, the CM product yield was improved over that obtained using standard Grubbs' catalyst reaction conditions (entry 4 vs 7). Notably, a single geometrical trans isomer was observed under these reaction conditions.[14]

More workable quantities of the key intermediate **12** enabled the synthesis of tritylated azidophytosphingosine **16** in a relatively straightforward and efficient manner, as shown in Scheme 3. Catalytic hydrogenation (Pd/C, H_2) of **12** readily yielded saturated ester **17** in 85% yield. The conversion of hydroxyl group in **17** to azide **18** with the inversion of configuration was achieved by triflate activation with Tf_2O, followed by a reaction with TMGA at 30 °C.[5a,b] Reduction of methyl ester **18** by the slow addition of diisobutylaluminium hydride (DIBAL) in toluene at −78 °C gave the aldehyde **19** in a reasonable 66% yield. Treatment of the phosphonium salt $Ph_3P^+CH_3Br^-$ with lithium hexamethyldisilazide (LHMDS) at 0 °C generated the ylide, which was then reacted with **19** furnished the cross-metathesis precursor **16** in 71% yield.

Table 2. Cross-metathesis reaction onto model olefin **6** with methyl acrylate

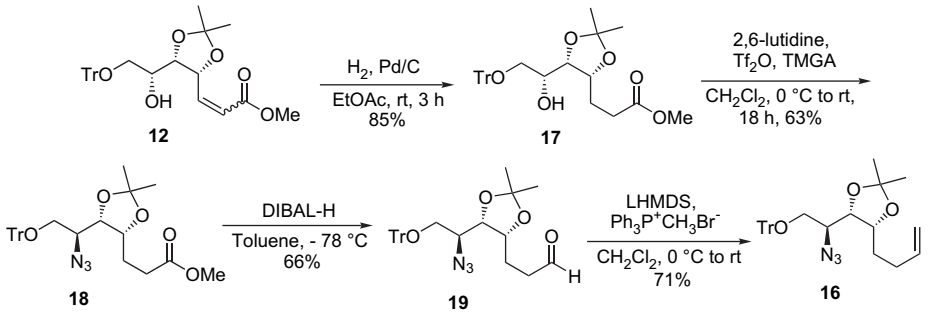


6

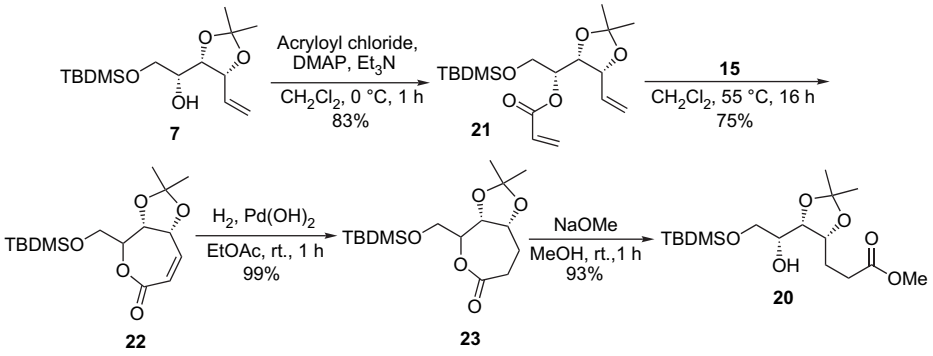
***E*-12**

15

Entry	Methyl acrylate (equiv)	Catalyst (equiv)	Solvent	Temperature (°C)	Yields (%)
1	2	0.05	CH_2Cl_2	rt	20
2	20	0.05	CH_2Cl_2	rt	31
3	2	0.1	CH_2Cl_2	Reflux	23
4	10	0.1	CH_2Cl_2	Reflux	37
5	2	0.1+0.3 $Ti(O^iPr)_4$	Toluene	80	25
6	10	0.1+0.3 $Ti(O^iPr)_4$	Toluene	Reflux	15
7	10	0.1+0.3 $Ti(O^iPr)_4$	Toluene	75	43



Scheme 3. Synthesis of olefin cross-metathesis building block **16**.



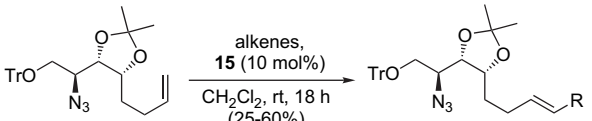
Scheme 4. Ring-closing metathesis reaction onto **7**.

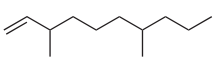
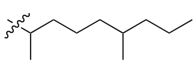
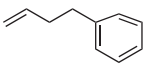
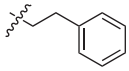
Alternatively, compound **20**, TBDMS protected analog of key intermediate **17**, was synthesized by ring-closing metathesis (RCM) approach, as illustrated in Scheme 4. The hydroxyl group of **7** reacted with acryloyl chloride generated **21** (83%) to set the stage for RCM reaction. Metathesis of terminal olefins of **21** was achieved by using catalyst **15** in CH_2Cl_2 at 55 °C to give α,β-unsaturated lactone **22** in 75% yield. The double bond was catalytically reduced ($Pd(OH)_2$, H_2) to afford lactone **23**, in quantitative yield, which underwent basic ring opening (NaOMe in methanol) to provide the methyl ester **20** in 93% yield.

With the successful outcome of the cross-metathesis reaction onto alkene **6** and methyl acrylate, we subsequently examined the effectiveness of azide-containing building block **16** as a coupling partner. The results of our small phytosphingosine library are summarized in Table 3. Initially, alkene **16** reacted with 1-heptadecene (entry 1) in the presence of catalyst **15** (10 mol %) in dichloromethane (0.1 M, **16**/1-heptadecene=1:10) at room temperature and the trans isomer **2a** was isolated in 59% yield. Then, selected terminal olefins were further processed in the CM to test the generality of our protocol. The results in Table 3 demonstrate that our synthetic strategy is efficient for synthesizing phytophingosine analogs with various lengths in the lipid chain. Cross-metathesis reaction with other linear alkenes (entries 2 and 3) afforded **2b–c** in isolated yields ranging between 57% and 60%, whereas branched terminal olefin (entry 4) resulted **2d** in a low CM yield (25%). For alkenes with phenyl and bromide substituents gave the corresponding substituted CM products **2e–f** (entries 5 and 6) in a reasonable 57% and 56% isolated yield, respectively. Notably, trans isomers were observed as major products with very trace amount of cis isomers based on the ^1H NMR characterization. It has been reported that the presence of the azido functional group caused the failure of cross-metathesis reactions.[8b,15] In contrast, increasing the distance between azide and reaction terminal olefin facilitated the building block **16** to undergo cross-metathesis to afford the suitably protected phytosphingosine analogs in moderate to good yields. Furthermore, although excess lipid alkenes were used to obtain reasonable yields of products in these experiments, no tractable homodimers were found.

In summary, the core building block **16** was obtained in seven-step manipulation from commercially available

Table 3. Synthesis of phytosphingosine library (**2a–f**) by olefin cross-metathesis reaction of **16** with various alkenes



Entry	Alkene	Product (**2**)	Yield (%)
1		**2a R** = 	59
2		**2b R** = 	57
3		**2c R** = 	60
4		**2d R** = 	25
5		**2e R** = 	57
6		**2f R** = 	56

D-lyxose. Compound **16** was further used to achieve the synthesis of suitably protected phytosphingosines with various lengths and substitutions in lipid chains. CM of **16** with alkenes catalyzed by Grubbs' catalyst (II) gave heterodimers in moderate yields. This procedure is flexible for synthesizing a phytosphingolipid library and provides a clear avenue for elucidating structure–activity relationships[16] for this class of biomolecules.

3. Experimental

3.1. General

All commercial materials were used without further purification unless otherwise noted. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride under N_2. THF was distilled from sodium/benzophenone ketyl radical under N_2. Analytical thin layer chromatography was performed on E. Merck silica gel 60 F_{254} plates (0.25 mm). Liquid column chromatography was performed using forced flow of the indicated solvent on silica gel 60 (E. Merck Co.). NMR spectra were recorded on either Bruker 400 or Bruker 500 MHz instruments and are reported in parts per million (δ) units. Coupling constants (J) are reported in hertz (Hz). Assignment of ^{1}H NMR spectra was achieved using 2D methods (COSY). High-resolution mass spectra were obtained by means of a Micromass (Autospec) mass spectrometer. All reactions were carried out in oven-dried glasswares (120 °C) under an atmosphere of nitrogen unless otherwise indicated. The Grubb's II catalyst used in the metathesis reactions was purchased from Aldrich.

3.1.1. (2*S*,3*S*,4*R*)-2-Azido-4,5-di-*O*-isopropylidene-1-trityloxy-tricos-7-ene (2a). To a solution of alkene **16** (19 mg, 39.3 μmol) in de-oxygenated CH_2Cl_2 (393 μL, 0.1 M for CM reaction) was added 1-heptadecene (119 μL, 393 μmol) under nitrogen. To the resulting mixture was added catalyst **15** (4 mg, 3.93 μmol) and then stirred at room temperature for 18 h. The solvent was evaporated to give brown residues. The crude residues were subjected to flash silica gel column chromatography to give **2a** (16 mg, 59%) as a colorless oil. R_f 0.27 (hexanes/EtOAc=20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J=7.0 Hz, 3H), 1.18–1.41 (m, 28H), 1.25 (s, 6H), 1.47–1.70 (m, 2H overlapped with H_2O), 1.94–2.11 (m, 3H), 2.16–2.27 (m, 1H), 3.35 (dd, J=7.6, 9.7 Hz, 1H), 3.48 (ddd, J=2.4, 7.6, 9.1 Hz, 1H), 3.53 (dd, J=2.4, 9.7 Hz, 1H), 3.87 (dd, J=5.5, 9.1 Hz, 1H), 4.11 (ddd, J=3.7, 5.5 10.0 Hz, 1H), 5.4 (ddd, J=6.1, 6.1, 15.4 Hz, 1H), 5.46 (ddd, J=6.1, 6.1, 15.4 Hz, 1H), 7.2–7.35 (m, 10H), 7.45–7.51 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.6, 28.0, 29.2, 29.2, 29.3, 29.4, 29.6, 29.6, 29.7, 29.7, 31.9, 32.6, 60.7, 64.5, 75.8, 77.2, 87.3, 108.1, 127.1, 128.8, 128.7, 128.9, 131.5, 143.8. HRMS (FAB) calcd for $C_{45}H_{64}NO_3$ (M−2N+H$^+$): 666.4886. Found: 666.4886.

Compounds **2b–f** were synthesized by following the method described in the synthesis of **2a**.

3.1.2. (2*S*,3*S*,4*R*)-2-Azido-3,4-di-*O*-isopropylidene-1-trityloxy-pentadec-7-ene (2b). Yield 57%. R_f 0.20 (hexanes/EtOAc=20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (t, J=7.0 Hz, 3H), 1.18–1.40 (m, 16H), 1.45–1.69 (m, 2H overlapped with H_2O), 1.96–2.26 (m, 4H), 3.35 (dd, J=7.6, 9.6 Hz, 1H), 3.48 (ddd, J=2.4, 7.6, 9.1 Hz, 1H), 3.53 (dd, J=2.4, 9.6 Hz, 1H), 3.87 (dd, J=5.5, 9.2 Hz, 1H), 4.11 (ddd, J=3.6, 5.5, 9.4 Hz, 1H), 5.41 (ddd, J=6.0, 6.0, 15.4 Hz, 1H), 5.46 (ddd, J=6.1, 6.1, 15.4 Hz, 1H), 7.20–7.34 (m, 10H), 7.44–7.51 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.7, 28.0, 29.2, 29.2, 29.3, 29.6, 31.9, 32.6, 60.7, 64.5, 75.8, 77.2, 87.3, 108.1, 127.1, 127.8, 128.7, 129.0, 131.5, 143.8. HRMS (FAB) calcd for $C_{37}H_{48}NO_3$ (M−2N+H$^+$): 554.3624. Found: 554.3634.

3.1.3. (2*S*,3*S*,4*R*)-2-Azido-3,4-di-*O*-isopropylidene-1-trityloxy-octadec-7-ene (2c). Yield 60%. R_f 0.20 (hexanes/EtOAc=20:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J=7.1 Hz, 3H), 1.17–1.40 (m, 22H), 1.48–1.68 (m, 2H overlapped with H_2O), 1.93–2.12 (m, 3H), 2.18–2.27 (m, 1H), 3.35 (dd, J=7.7, 9.9 Hz, 1H), 3.48 (ddd, J=2.4, 7.7, 9.3 Hz, 1H), 3.53 (dd, J=2.4, 9.9 Hz, 1H), 3.87 (dd, J=5.5, 9.3 Hz, 1H), 4.11 (ddd, J=3.7, 5.5, 10.1 Hz, 1H), 5.41 (ddd, J=6.4, 6.4, 15.5 Hz, 1H), 5.46 (ddd, J=6.4, 6.4, 15.5 Hz, 1H), 7.20–7.36 (m, 10H), 7.43–7.54 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.7, 25.7, 28.0, 29.2, 29.2, 29.3, 29.4, 29.6, 29.6, 29.7, 31.9, 32.6, 60.7, 64.5, 75.8, 87.3, 108.1, 127.1, 127.9, 128.7, 128.9, 131.5, 143.8. HRMS (FAB) calcd for $C_{40}H_{53}N_3O_3$ (M$^+$): 623.4087. Found: 623.4087.

3.1.4. (2*S*,3*S*,4*R*)-2-Azido-3,4-di-*O*-isopropylidene-9,13-dimethyl-1-trityloxy-hexadec-7-ene (2d). Yield 25%. R_f 0.50 (hexanes/EtOAc=20:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.78 (s, 3H), 0.79 (s, 3H), 0.81 (d, J=7 Hz, 3H), 0.88 (d, J=7 Hz, 3H), 1.05–1.18 (m, 9H), 1.40–1.62 (m, 4H overlapped with H_2O), 1.97–2.07 (m, 3H), 2.12–2.25 (m, 2H), 3.40 (ddd, J=4.4, 9.5, 14.2 Hz, 1H), 3.78–3.96 (m, 4H), 4.13 (ddd, J=4.0, 5.6, 9.6 Hz, 1H), 5.26 (dd, J=1.2, 10 Hz, 1H), 5.31 (ddd, J=5.3, 5.3, 10 Hz, 1H), 7.17–7.40 (m, 15H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.8, 28.1, 29.3, 29.4, 34.5, 36.2, 60.8, 64.6, 75.9, 77.5, 125.9, 127.2, 127.9, 128.0, 128.4, 128.6, 128.9, 129.8, 130.0, 130.5, 142.2, 143.9. HRMS (FAB) calcd for $C_{40}H_{53}N_3O_3Na$ (M$^+$+Na): 646.3997. Found: 646.3997.

3.1.5. (2*S*,3*S*,4*R*)-2-Azido-3,4-di-*O*-isopropylidene-10-phenyl-dec-7-ene (2e). Yield 57%. R_f 0.50 (hexanes/EtOAc=20:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.15 (s, 3H), 1.17 (s, 3H), 1.36–1.58 (m, 2H), 1.94–2.19 (m, 2H), 2.26 (td, J=6.0, 7.6 Hz, 2H), 2.61 (t, J=7.6 Hz, 2H), 3.3 (dd, J=7.6, 9.8 Hz, 1H), 3.4 (ddd, J=2.4, 7.4, 9.4 Hz, 1H), 3.46 (dd, J=2.4, 9.8 Hz, 1H), 3.79 (dd, J=5.6, 9.3 Hz, 1H), 3.99 (ddd, J=3.9, 5.6, 9.8 Hz, 1H), 5.37 (ddd, J=6.0, 6.0, 15.4 Hz, 1H), 5.44 (ddd, J=6.0, 6.0, 15.4 Hz, 1H), 7.09–7.25 (m, 15H), 7.37–7.43 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.8, 22.4, 22.6, 22.6, 24.6, 25.0, 25.5, 27.9, 28.0, 29.2, 29.3, 36.7, 37.3, 39.0, 61.1, 61.8, 63.1, 63.9, 77.0, 82.0, 108.4, 126.8, 126.9, 127.0, 127.2, 127.7, 127.7, 127.9, 128.7, 129.6, 137.7, 146.8. HRMS (FAB) calcd for $C_{38}H_{42}NO_3$ (M−2N+H$^+$): 560.3165. Found: 560.3162.

3.1.6. (2*S*,3*S*,4*R*)-2-Azido-10-bromo-3,4-di-*O*-isopropylidene-1-trityloxy-dec-7-ene (2f). Yield 56%. R_f 0.18

(hexanes/EtOAc=20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (s, 3H), 1.25 (s, 3H), 1.49–1.71 (m, 2H overlapped with H_2O), 2.08–2.13 (m, 1H), 2.23–2.29 (m, 1H), 2.57 (td, J=6.8, 7.2 Hz, 2H), 3.36 (dd, J=7.6, 10.8 Hz, 1H), 3.38 (dd, J=7.2, 9.8 Hz, 2H), 3.48 (ddd, J=2.5, 7.1, 9.4 Hz, 1H), 3.53 (dd, J=2.5, 9.8 Hz, 1H), 3.88 (dd, J=5.5, 9.4 Hz, 1H), 4.11 (ddd, J=3.5, 5.5, 9.8 Hz, 1H), 5.46 (ddd, J=6.6, 6.6, 15.3 Hz, 1H), 5.56 (ddd, J=6.6, 6.6, 15.3 Hz, 1H), 7.21–7.34 (m, 10H), 7.45–7.51 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7, 28.0, 28.9, 29.2, 32.8, 36.0, 60.7, 64.5, 75.7, 77.2, 87.3, 108.2, 127.1, 127.5, 127.9, 128.7, 132.7, 143.7.

3.1.7. 5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-α/β-D-lyxofuranose (5). To a magnetically stirred solution of 2,3-*O*-isopropylidene-D-lyxofuranose[4a] (160 mg, 0.84 mmol) in DMF (1.6 mL) at 0 °C were added imidazole (114 mg, 1.68 mmol) and *tert*-butyldimethylsilyl chloride ((127 mg, 0.84 mmol) under argon. The reaction was then slowly warmed to room temperature and stirred for 9 h at ambient temperature. The solution was concentrated and the residue was dissolved in EtOAc. The organic layer was successively washed with water and brine, dried with $MgSO_4$, and filtered. The solution was concentrated and the residue was purified by silica gel column chromatography to afford **5** (258 mg, 71%) as a yellowish oil (hexanes/EtOAc=8:1–4:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.08 (s, Me, 3H), 0.90 (s, ^{t}Bu, 9H), 1.30 (s, Me, 3H), 1.43 (s, Me, 3H), 3.81 (dd, $J_{5a,5b}$=10.8 Hz, $J_{5a,4}$=7.2 Hz, H-5a, 1H), 3.92 (dd, $J_{5b,5a}$=10.8 Hz, $J_{5b,4}$=4.6 Hz, H-5b, 1H), 4.23 (ddd, $J_{4,5a}$=7.2 Hz, $J_{4,5b}$=4.6 Hz, $J_{4,3}$=3.7 Hz, H-4, 1H), 4.58 (d, $J_{2,3}$=5.9 Hz, H-2, 1H), 4.74 (dd, $J_{3,2}$=5.9 Hz, $J_{3,4}$=3.7 Hz, H-3, 1H), 5.39 (s, H-1, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.12, −5.04, 18.69, 25.11, 26.14×3, 26.19, 26.30, 61.76, 80.02, 81.40, 85.72, 101.50. HRMS (FAB) calcd for $C_{14}H_{29}O_5Si$ (M+H$^+$): 305.1783. Found: 305.1784.

3.1.8. (2*R*,3*R*,4*R*)-2-Hydroxyl-3,4-*O*-isopropylidene-1-trityloxy-hex-5-ene (6). Lithium hexamethyldisilazane (LHMDS) (22.7 mL of 1.0 M solution in THF) was added to a solution of triphenyl-tridecyl-phosphonium bromide (8.14 g, 22.7 mmol) in anhydrous THF (100 mL) at 0 °C under nitrogen. After being stirred at 0 °C for 1 h, a solution containing LHMDS (15.2 mL of 1.0 M in THF) and 5-trityloxy-2,3-*O*-isopropylidene-D-lyxofuranose **4**[5b] (6.57 g, 15.2 mmol) in THF (100 mL) was slowly added at 0 °C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for 9 h. After quenching the reaction with methanol, the solvent was removed in vacuo. The resulting residues were dissolved in EtOAc and washed with H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated to dryness. The crude material was purified by silica gel column chromatography to afford **6** (5.37 g; 82%) as white solid. R_f 0.30 (hexanes/EtOAc=3:1); mp=79.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.49 (s, 3H), 2.36 (d, J=6.2 Hz, 1H), 3.14 (dd, J=5.8, 9.6 Hz, 1H), 3.23 (dd, J=4.9, 9.6 Hz, 1H), 3.71 (ddd, J=4.7, 4.9, 5.8 Hz, 1H), 4.29 (dd, J=4.7, 6.8 Hz, 1H), 4.45 (dd, J=6.8, 8.3 Hz, 1H), 5.12 (dd, J=18.5 Hz, 1H), 5.13 (dd, J=10.3 Hz, 1H), 5.87 (ddd, J=8.3, 10.3, 18.5 Hz, 1H), 7.19–7.38 (m, 10H), 7.41–7.55 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.09, 27.36, 64.68, 69.19, 77.73, 79.08, 86.73, 108.71, 119.43, 127.07, 127.85, 128.72, 134.04, 143.84. HRMS (FAB) calcd for $C_{28}H_{30}O_4$ (M$^+$): 430.2144. Found: 430.2144.

3.1.9. (2*R*,3*R*,4*R*)-1-*O*-(*tert*-Butyldimethylsilyl)-2-hydroxyl-3,4-*O*-isopropylidene-hex-5-ene (7).[17] This compound was similarly prepared as that described for **6**. Starting from 5-*tert*-butyldimethylsilyloxy-2,3-*O*-isopropylidene-D-lyxofuranose **5** (3.42 g, 11.2 mmol), pure compound **7** (2.52 g) was isolated as a light oil in 78% yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.048 (s, 3H), 0.051 (s, 3H), 0.88 (s, 9H), 1.38 (s, 3H), 1.51 (s, 3H), 3.60 (m overlapped with s at 3.59 ppm, $J_{2,3}$=3.3 Hz, H-1, H-2, 3H), 4.23 (dd, $J_{3,4}$=7.5 Hz, $J_{3,2}$=3.3 Hz, H-3, 1H), 4.58 (t, $J_{4,3}$=7.5 Hz, $J_{4,5}$=7.5 Hz, H-4, 1H), 5.27 (d, $J_{6a,6b}$=10.2 Hz, H-6a, 1H), 5.33 (d, $J_{6b,5}$=17.2 Hz, H-6b, 1H), 6.04 (ddd, $J_{5,6b}$=17.2 Hz, $J_{5,6a}$=10.2 Hz, $J_{5,4}$=7.5 Hz, H-5, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.16×2, 18.54, 25.18, 26.10×3, 27.42, 64.39, 70.18, 79.35, 108.87, 119.57, 134.71. HRMS (FAB) calcd for $C_{15}H_{31}O_4Si$ (M+H$^+$): 303.1996. Found: 303.1992.

3.1.10. (2*R*,3*R*,4*R*)-3,4-*O*-Isopropylidene-1-trityloxy-hexane-2-ol (10). Palladium on charcoal (Pd/C) (100 mg; 5% Pd content) was suspended to a solution of **6** (150 mg, 0.35 mmol) in EtOAc (5.0 mL). The flask was purged with H_2, and a hydrogen balloon was attached. After 1 h, the catalyst was filtered off through a pad of Celite, the solvent was removed in vacuo, and the residue was purified by flash silica gel column chromatography to give **10** (149 mg; quantitative) as a yellow solid. R_f 0.32 (hexanes/EtOAc=3:1); mp=115.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.96 (t, J=7.4 Hz, 3H), 1.36 (s, 3H), 1.41–1.50 (m, 3H), 1.45 (s, 3H), 1.62–1.73 (m, 1H), 2.30 (d, J=6.0 Hz, 1H), 3.19 (dd, J=5.7, 9.6 Hz, 1H), 3.22 (dd, J=6.0, 9.6 Hz, 1H), 3.72 (ddd, J=3.8, 5.7, 6.0 Hz, 1H), 4.00 (ddd, J=4.2, 6.3, 10.0 Hz, 1H), 4.15 (dd, J=3.8, 6.3 Hz, 1H), 7.20–7.36 (m, 10H), 7.40–7.51 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.10, 22.87, 25.22, 27.39, 65.28, 68.90, 78.97, 86.87, 107.76, 127.06, 127.83, 128.73, 143.91. HRMS (FAB) calcd for $C_{28}H_{32}O_4$ (M$^+$): 432.2309. Found: 432.2301.

3.1.11. (2*S*,3*S*,4*R*)-2-Azido-4,5-di-*O*-isopropylidene-1-trityloxy-hexane (11). To a stirred solution of **10** (66 mg, 0.15 mmol) in dry CH_2Cl_2 (1.0 mL) with freshly activated 4 Å MS (20 mg) was added 2,6-lutidine (35 μL, 8.81 mmol). The reaction mixture was cooled to −40 °C and TMSOTf (38 μL, 0.23 mmol) was added to it. After being stirred at −40 °C for 30 min, tetramethylguanidinium azide (72 mg, 0.46 mmol) was added and stirred at the same temperature for an additional 30 min. The reaction mixture was allowed to warm to room temperature for over 18 h. The reaction mixture was diluted with EtOAc, filtered, and washed with H_2O and brine. Following drying ($MgSO_4$) and concentration, the crude product was purified by flash silica gel chromatography to afford **11** (50 mg; 72%) as a yellow oil. R_f 0.50 (hexanes/EtOAc=3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (t, J=7.4 Hz, 3H), 1.23 (s, 3H), 1.26 (s, 3H), 1.42–1.53 (m, 1H), 1.59–1.70 (m, 1H), 3.36 (dd, J=7.9, 9.9 Hz, 1H), 3.47 (ddd, J=2.2, 7.9, 9.3 Hz, 1H), 3.53 (dd, J=2.2, 9.9 Hz, 1H), 3.89 (dd, J=5.5, 9.3 Hz, 1H), 4.02 (ddd, J=4.1, 5.5, 9.6 Hz, 1H), 7.19–7.40 (m, 10H), 7.43–7.55 (m, 5H). ^{13}C NMR (125 MHz,

$CDCl_3$): δ 10.93, 22.45, 25.66, 28.01, 60.74, 64.56, 75.80, 79.41, 87.28, 108.13, 127.07, 127.84, 128.73, 143.77. HRMS (FAB) calcd for $C_{28}H_{31}N_3O_3$ (M^+): 457.2361. Found: 457.2365.

3.1.12. (4*R*,5*R*,6*R*)-Methyl *Z*-2,3-dideoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-lyxo-2-heptenonate (*Z*-12). A mixture of 5-trityloxy-2,3-*O*-isopropylidene-D-lyxofuranose **4**[5b] (4.65 g, 10.70 mmol) and methyl(triphenylphosphoranylidene)acetate (7.20 g, 21.50 mmol) in dry CH_2Cl_2 (50 mL) was stirred for 13 h at room temperature under nitrogen. Volatiles were removed under reduced pressure. The resulting residues were dissolved in EtOAc and then washed with water and brine, dried ($MgSO_4$), filtered, and concentrated. Flash silica gel column chromatography yielded *Z*-**12** (1.92 g; 36%) as a white solid. Mp=122 °C; R_f 0.33 (hexanes/EtOAc=3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.50 (s, 3H), 2.16 (d, *J*=8.5 Hz, 1H), 3.14 (dd, *J*=5.7, 9.4 Hz, 1H), 3.20 (dd, *J*=6.7, 9.4 Hz, 1H), 3.51–3.61 (m, 1H), 3.71 (s, 3H), 4.59 (dd, *J*=1.6, 7.7 Hz, 1H), 5.61 (ddd, *J*=1.5, 6.9, 7.7 Hz, 1H), 5.90 (dd, *J*=1.5, 11.6 Hz, 1H), 6.50 (dd, *J*=6.9, 11.6 Hz, 1H), 7.18–7.37 (m, 10H), 7.40–7.50 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.3, 26.7, 51.5, 65.5, 68.6, 75.0, 78.2, 86.2, 108.9, 120.7, 127.0, 127.8, 128.7, 144.0, 148.0, 166.2. HRMS (FAB) calcd for $C_{30}H_{32}O_6$ (M^+): 488.2202. Found: 488.2199.

3.1.13. (4*R*,5*R*,6*R*)-Methyl *E*-2,3-dideoxy-4,5-*O*-isopropylidene-7-*O*-trityl-D-lyxo-2-heptenonate (*E*-12). This compound was prepared by cross-metathesis reaction of alkene **6** and methyl acrylate in refluxing CH_2Cl_2. Typically, to a solution of **5** (150 mg, 0.35 mmol) in dry CH_2Cl_2 (7.0 mL, 0.05 M for CM reaction) were added methyl acrylate (314 μL, 3.84 mmol) and Grubb's II catalyst **15** (30 mg, 35.0 μmol) at room temperature under nitrogen. After being refluxed for 13 h, the reaction mixture was evaporated to dryness. The crude material was purified by silica gel flash column chromatography to afford pure compound *E*-**12** (62 mg; 37%) as a white solid. R_f 0.33 (hexanes/EtOAc=3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 3H), 1.49 (s, 3H), 2.27 (d, *J*=6.5 Hz, 1H), 3.12 (dd, *J*=5.6, 9.6 Hz, 1H), 3.22 (dd, *J*=5.3, 9.6 Hz, 1H), 3.64 (ddd, *J*=4.5, 5.3, 4.5 Hz, 1H), 3.71 (s, 3H), 4.38 (dd, *J*=4.5, 6.9 Hz, 1H), 4.56 (dd, *J*=6.9, 7.0 Hz, 1H), 5.85 (d, *J*=15.7 Hz, 1H), 6.85 (dd, *J*=7.0, 15.7 Hz, 1H), 7.18–7.34 (m, 10H), 7.37–7.49 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.14, 27.28, 51.67, 64.61, 68.84, 76.51, 78.09, 86.87, 109.46, 123.26, 127.15, 127.90, 128.66, 143.35, 143.70, 166.08. HRMS (FAB) calcd for $C_{30}H_{32}O_6Na$ (M+Na^+): 511.2087. Found: 511.2097.

3.1.14. (2*S*,3*S*,4*R*)-2-Azido-3,4-di-*O*-isopropylidene-1-trityloxy-oct-7-ene (16). LHMDS (372 μL of 1 M solution in THF) was added to a solution of methyltriphenylphosphonium bromide (121 mg, 0.34 mmol) in dry THF (2.0 mL) at 0 °C under nitrogen and the resulting mixture was stirred for 1 h. A solution containing the aldehyde **19** (150 mg, 0.31 mmol) in dry THF (2.5 mL) was added slowly at 0 °C to the above mixture. The reaction mixture was warmed to room temperature and stirred for 9 h, and then quenched with MeOH. The solvents were removed in vacuo. The resulting residues were diluted with EtOAc and washed with H_2O and brine. The crude residues were dried with $MgSO_4$ and concentrated to dryness. The crude residues were purified by flash silica gel column chromatography to afford pure compound **16** (85 mg; 57%) as a yellow oil. R_f 0.21 (hexanes/EtOAc=20:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.24 (s, 3H), 1.50–1.60 (m, 1H overlapped with H_2O), 1.62–1.71 (m, 1H), 2.07–2.16 (m, 1H), 2.23–2.33 (m, 1H), 3.34 (dd, *J*=7.7, 9.9 Hz, 1H), 3.46 (ddd, *J*=2.5, 7.7, 9.4 Hz, 1H), 3.52 (dd, *J*=2.5, 9.9 Hz, 1H), 3.87 (dd, *J*=5.6, 9.4 Hz, 1H), 4.10 (ddd, *J*=3.5, 5.6, 10.3 Hz, 1H), 4.98 (br dd, *J*=1.7, 10.2 Hz, 1H), 5.04 (br dd, *J*=1.7, 16.9 Hz, 1H), 5.83 (dddd, *J*=6.6, 6.6, 10.2, 16.9 Hz, 1H), 7.19–7.35 (m, 10H), 7.43–7.52 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.7, 28.0, 28.6, 30.5, 60.7, 64.5, 75.8, 87.3, 108.2, 115.1, 127.1, 127.9, 128.7, 137.9, 143.8. HRMS (FAB) calcd for $C_{30}H_{34}N_3O_3$ (M+H^+): 484.2588. Found: 484.2600.

3.1.15. (4*R*,5*R*,6*R*)-6-Hydroxy-4,5-di-*O*-isopropylidene-7-trityloxy-heptanoic acid methyl ester (17). To a stirred solution of **12** (236 mg, 0.48 mmol) in EtOAc (5.0 mL) was added a catalytic amount of palladium (5 wt % on activated C). Then, the mixture was degassed by hydrogen and then stirred at room temperature for 1 h under hydrogen. The crude residues were purified by flash silica gel column chromatography to afford pure compound **17** (222 mg, 94 %) as a yellow syrup. R_f 0.24 (hexanes/EtOAc=3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.42 (s, 3H), 1.75 (dddd, *J*=2.9, 8.7, 10.2, 13.9 Hz, 1H), 1.96 (dddd, *J* =5.6, 8.5, 10.7, 13.9 Hz, 1H), 2.26 (d, *J*=6.5 Hz, 1H), 2.34 (ddd, *J*=8.5, 10.2, 16.2 Hz, 1H), 2.50 (ddd, *J*=5.6, 8.7, 16.2 Hz, 1H), 3.18 (dd, *J*=5.8, 9.5 Hz, 1H), 3.22 (dd, *J*=6.0, 9.5 Hz, 1H), 3.65 (s, 3H), 3.72 (dddd, *J*=3.7, 5.8, 6.0, 6.5 Hz, 1H), 4.07 (ddd, *J*=2.9, 6.4, 10.6 Hz, 1H), 4.17 (dd, *J*=3.7, 6.4 Hz, 1H), 7.18–7.34 (m, 10H), 7.39–7.47 (m, 5H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.2, 25.5, 27.4, 31.0, 51.6, 65.2, 68.8, 76.3, 76.9, 86.9, 108.1, 127.1, 127.9, 128.7, 143.8, 173.7. HRMS (FAB) calcd for $C_{30}H_{34}O_6Na$ (M+Na^+): 513.2254. Found: 513.2253.

3.1.16. (4*R*,5*S*,6*S*)-6-Azido-4,5-di-*O*-isopropylidene-7-trityloxy-heptanoic acid methyl ester (18). To a stirred solution of **17** (1.44 g, 2.94 mmol) and freshly activated 4 Å MS (60 mg) in dry CH_2Cl_2 (30 mL) was added 2,6-lutidine (1.03 mL, 8.81 mmol). The reaction mixture was cooled to −40 °C and TMSOTf (993 μL, 5.88 mmol) was added to it. After being stirred at −40 °C for 30 min, tetramethylguanidinium azide (1.4 g, 8.81 mmol) was added and stirred at the same temperature for an additional 30 min. The reaction mixture was allowed to warm to room temperature for over 18 h. The reaction mixture was diluted with EtOAc, filtered, and washed with H_2O and brine. Following drying ($MgSO_4$) and concentration, the crude product was purified by flash silica gel chromatography to afford **18** (1.39 g, 92%) as a yellow oil. R_f 0.50 (hexanes/EtOAc=3:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.25 (s, 6H), 1.70–1.79 (m, 1H), 1.91–2.01 (m, 1H), 2.42 (ddd, *J*=7.0, 8.6, 16.2 Hz, 1H), 2.54 (ddd, *J*=5.7, 9.0, 16.2 Hz, 1H), 3.39 (dd, *J*=7.3, 9.9 Hz, 1H), 3.46 (ddd, *J*=2.4, 7.3, 9.6 Hz, 1H), 3.55 (dd, *J*=2.4, 9.9 Hz, 1H), 3.69 (s, 3H), 3.96 (dd, *J*=5.6, 9.6 Hz, 1H), 4.11 (ddd, *J*=3.1, 5.6, 10.8 Hz, 1H), 7.21–7.35 (m, 10H), 7.45–7.52 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.1, 25.7, 28.0, 30.8, 51.6, 60.2, 64.4, 75.5, 77.2, 87.3,

108.6, 127.1, 127.9, 128.7, 143.7, 173.7. HRMS (FAB) calcd for $C_{30}H_{33}N_3O_5Na$ (M+Na$^+$): 538.2308. Found: 538.2318.

3.1.17. (4*R*,5*S*,6*S*)-6-Azido-4,5-di-*O*-isopropylidene-7-trityloxy-heptanal (19). DIBAL (1.25 mL of 1 M solution in toluene) was added dropwise to a solution of compound **18** (429 mg, 0.83 mmol) in toluene (12 mL) at −78 °C for 6 h. The reaction mixture was quenched with MeOH and then warmed to room temperature. The resulting residues were concentrated to dryness and purified by flash silica gel column chromatography to afford pure compound **19** (291 mg, 70%) as a yellow oil. R_f 0.40 (hexanes/EtOAc=3:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.25 (s, 6H), 1.74 (dddd, J=6.2, 7.9, 10.9, 14.0 Hz, 1H), 1.95 (dddd, J=3.1, 6.7, 8.1, 14.0 Hz, 1H), 2.52–2.72 (m, 2H), 3.40 (dd, J=7.2, 9.7 Hz, 1H), 3.47 (ddd, J=2.2, 7.2, 9.4 Hz, 1H), 3.55 (dd, J=2.2, 9.7 Hz, 1H), 3.97 (dd, J=5.6, 9.4 Hz, 1H), 4.10 (ddd, J=3.1, 5.6, 10.9 Hz, 1H), 7.21–7.35 (m, 10H), 7.45–7.51 (m, 5H), 9.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.4, 25.6, 28.0, 40.8, 60.2, 64.4, 75.5, 76.8, 87.4, 108.6, 127.1, 127.9, 128.7, 143.7, 201.7. HRMS (FAB) calcd for $C_{29}H_{32}NO_4$ (M−2N+H$^+$): 458.2324. Found: 458.2331.

3.1.18. (4*R*,5*R*,6*R*)-7-*O*-(*tert*-Butyldimethylsilyl)-4,5-di-*O*-isopropylidene-6-hydroxy-heptanoic acid methyl ester (20). To a solution of lactone **23** (205 mg, 0.62 mmol) in MeOH (5.0 mL) was added catalytic amount of NaOMe (3.3 mg, 0.062 mmol). After 10 min of stirring at 25 °C, the reaction mixture was neutralized with acidic resin. The resin was filtered off and the filtrate was concentrated. The residue after silica gel column chromatography afforded title compound **20** (210 mg, 94%) as light oil (hexanes/EtOAc=9:1–7:1). $[\alpha]_D^{26}$ −3.25 (*c* 1.04, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.08 (s, 6H), 0.91 (s, ^{t}Bu, 9H), 1.36 (s, Me, 3H), 1.49 (s, Me, 3H), 1.89–1.96 (m, H-3a, 1H), 2.02–2.09 (m, H-3b, 1H), 2.40–2.47 (m, $J_{2a,2b}$=16.3 Hz, H-2a, 1H), 2.54–2.61 (m, $J_{2b,2a}$=16.3 Hz, H-2b, 1H), 3.60 (dd, $J_{7a,7b}$=9.7 Hz, $J_{7a,6}$=6.5 Hz, H-7a, 1H), 3.66 (dd, $J_{7b,7a}$=9.7 Hz, $J_{7b,6}$=5.9 Hz, H-7b, 1H), 3.67–3.73 (m overlapped with s at 3.69 ppm, $J_{6,7a}$=6.5 Hz, $J_{6,7b}$=5.9 Hz, H-6, Me, 4H), 4.14–4.20 (m overlapped with d at 4.16 ppm, H-4, H-5, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.22×2, 18.49, 25.39, 25.81, 26.07×3, 27.58, 31.11, 51.78, 64.75, 76.45, 76.76, 108.23, 173.95. HRMS (FAB) calcd for $C_{17}H_{35}O_6Si$ (M+H$^+$): 363.2206. Found: 363.2203.

3.1.19. (4*R*,5*R*,6*R*)-1,2-Dideoxy-3,4-di-*O*-isopropylidene-5-acryloxy-6-*O*-(*tert*-butyldimethylsilyl)-D-lyxohex-1-enitol (21). Acryloyl chloride (150 μL, 1.85 mmol) was added to a stirred solution of **7** (466 mg, 1.54 mmol), DMAP (19 mg, 0.15 mmol), and Et_3N (263 μL, 1.89 mmol) in CH_2Cl_2 (5.0 mL) under argon at 0 °C. After being stirred for 60 min, the reaction mixture was evaporated to dryness. The resulting residues were diluted with EtOAc and successively washed with H_2O and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated to dryness. The crude residues were purified by flash silica gel column chromatography to afford pure compound **21** (456 mg, 83%) as yellow oil (hexanes/EtOAc=16:1–12:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.52 (s, Me, 3H), 0.59 (s, Me, 3H), 0.89 (s, ^{t}Bu, 9H), 1.40 (s, Me, 3H), 1.54 (s, Me, 3H), 3.73 (d, $J_{1,2}$=5.9 Hz, H-1, 2H), 4.48 (dd, $J_{3,4}$=6.9 Hz, $J_{3,2}$=3.9 Hz, H-3, 1H), 4.67 (dddd, $J_{4,5}$=7.5 Hz, $J_{4,3}$=6.9 Hz, $J_{4,6}$=1.2 Hz, $J_{4,7}$=1.2 Hz, H-4, 1H), 4.92 (td, $J_{2,1}$=5.9 Hz, $J_{2,3}$=3.9 Hz, H-2, 1H), 5.24 (ddd, $J_{6b,5}$=10.3 Hz, $J_{6b,6a}$=1.3 Hz, $J_{6b,4}$=1.2 Hz, H-6b, 1H), 5.35 (ddd, $J_{6a,5}$=17.2 Hz, $J_{6a,6b}$=1.3 Hz, $J_{6a,4}$=1.2 Hz, H-6a, 1H), 5.80 (ddd, $J_{5,6a}$=17.2 Hz, $J_{5,6b}$=10.3 Hz, $J_{5,4}$=7.5 Hz, H-5, 1H), 5.85 (dd, $J_{3'b,2'}$=10.4 Hz, $J_{3'b,3'a}$=1.5 Hz, H-3′b, 1H), 6.14 (dd, $J_{2',3'a}$=17.2 Hz, $J_{2',3'b}$=10.4 Hz, H-2′, 1H), 6.44 (dd, $J_{3'a,2'}$=17.2 Hz, $J_{3'a,3'b}$=1.5 Hz, H-3′a, 1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ −5.26, −5.22, 18.44, 25.67, 26.02×3, 27.37, 61.49, 72.47, 75.99, 78.66, 109.13, 119.30, 128.82, 131.30, 133.51, 165.59. HRMS (FAB) calcd for $C_{18}H_{33}O_5Si$ (M+H$^+$): 357.2102. Found: 357.2097.

3.1.20. (4*R*,5*R*,6*R*)-7-(*tert*-Butyldimethylsilyl)-5,6-di-*O*-isopropylidene-6,7-dihydro-5*H*-oxepin-2-one (22). A solution of **21** (1.16 g, 3.3 mmol) in degassed CH_2Cl_2 (113 mL) containing catalyst **15** (278 mg, 0.33 mmol) was heated to reflux under nitrogen for 16 h. The reaction mixture was cooled to room temperature and treated with activated charcoal for 16 h after passing through a short silica gel bed. Charcoals were filtered off through Celite, and then concentrated under reduced pressure. Column chromatography on silica gel (hexanes/EtOAc=8:1–6:1) afforded 813 mg (75%) of **22** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.09 (s, Me, 3H), 0.10 (s, Me, 3H), 0.90 (s, ^{t}Bu, 9H), 1.37 (s, Me, 3H), 1.50 (s, Me, 3H), 3.84 (dd, $J_{7b,7a}$=10.1 Hz, $J_{7b,6}$=6.3 Hz, H-7b, 1H), 3.90 (dd, $J_{7a,7b}$=10.1 Hz, $J_{7a,6}$=7.3 Hz, H-7a, 1H), 4.18 (ddd, $J_{6,7a}$=7.3 Hz, $J_{6,7b}$=6.3 Hz, $J_{6,5}$=0.6 Hz, H-6, 1H), 4.48 (dd, $J_{5,4}$=6.7 Hz, $J_{5,6}$=0.6 Hz, H-5, 1H), 4.67 (dd, $J_{4,3}$=6.7 Hz, $J_{4,5}$=6.7 Hz, H-4, 1H), 6.24 (d, $J_{2,3}$=11.1 Hz, H-2, 1H), 6.68 (dd, $J_{3,2}$=11.1 Hz, $J_{3,4}$=6.7 Hz, H-3, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.29, −5.15, 18.50, 25.26, 25.55, 26.05×3, 61.44, 71.88, 77.48, 78.95, 109.78, 137.27, 166.81. HRMS (FAB) calcd for $C_{16}H_{29}O_5Si$ (M+H$^+$): 329.1783. Found: 329.1784.

3.1.21. (4*R*,5*R*,6*R*)-7-(*tert*-Butyldimethylsilanyloxymethyl)-5,6-di-*O*-isopropylidene-oxepan-2-one (23). Catalytic amount of $Pd(OH)_2$ (20% on active carbon) was suspended to a solution of **22** (321 mg, 0.98 mmol) in EtOAc (3.0 mL). The flask was purged with H_2, and a hydrogen balloon was attached. After 1 h, the catalyst was filtered off through a pad of Celite and the filtrate was concentrated to give lactone **23** (321 mg; 99%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.09 (s, Me, 3H), 0.10 (s, Me, 3H), 0.91 (s, ^{t}Bu, 9H), 1.37 (s, Me, 3H), 1.50 (s, Me, 3H), 2.03 (dddd, $J_{3a,3b}$=15.3 Hz, $J_{3a,2b}$=9.8 Hz, $J_{3a,2a}$=5.4 Hz, $J_{3a,4}$=2.6 Hz, H-3a, 1H), 2.29 (dddd, $J_{3b,3a}$=15.3 Hz, $J_{3b,2a}$=9.3 Hz, $J_{3b,2b}$=5.9 Hz, $J_{3b,4}$=5.9 Hz, H-3b, 1H), 2.73 (dd, $J_{2a,2b}$=13.6 Hz, $J_{2a,3b}$=9.3 Hz, $J_{2a,3a}$=5.4 Hz, H-2a, 1H), 2.76 (dd, $J_{2b,2a}$=13.6 Hz, $J_{2b,3a}$=9.8 Hz, $J_{2b,3b}$=5.9 Hz, H-2b, 1H), 3.81 (dd, $J_{7a,7b}$=10.0 Hz, $J_{7a,6}$=6.0 Hz, H-7a, 1H), 3.85 (dd, $J_{7b,7a}$=10.0 Hz, $J_{7b,6}$=7.2 Hz, H-7b, 1H), 4.27 (d, $J_{5,4}$=6.5 Hz, H-5, 1H), 4.28 (dd, $J_{6,7b}$=7.2 Hz, $J_{6,7a}$=6.0 Hz, H-6, 1H), 4.49–4.52 (m, $J_{4,5}$=6.5 Hz, $J_{4,3b}$=5.9 Hz, $J_{4,3a}$=2.6 Hz, H-4, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ −5.24, −5.15, 18.52, 20.63, 25.55, 25.99, 26.07×3, 28.23, 61.81, 74.15, 74.41, 77.43, 109.83, 171.76. HRMS (FAB) calcd for $C_{16}H_{31}O_5Si$ (M+H$^+$): 331.1946. Found: 331.1941.

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