Synthesis of *C*-Glycoside Analogs of the Immunostimulatory Glycosphingolipid, α-Galactosylceramide

by

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A dissertation submitted to the Graduate Faculty in Chemistry in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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Approval Page

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Abstract

Synthesis of *C*-Glycoside Analogs of the Immunostimulatory Glycosphingolipid, α-Galactosylceramide

by

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This dissertation presents the asymmetric total synthesis of immunostimulatory α-*C*-galactosylceramide (α-*C*-GalCer) glycolipids and D-*ribo*-phytosphingosine. Also included in this dissertation is an improved two-step synthetic route to primary allylic alcohols from aldehydes and verification of configurations of three contiguous stereogenic centers in the phytosphingosine backbone of α-1*C*-GalCer, the nonisosteric analog of α-*C*-GalCer in which the glycosidic oxygen atom linking the sugar with phytosphingosine is deleted..

Chapter 1 presents an improved two-step synthetic route to primary allylic alcohols from aldehydes. A modification of the Horner-Wadsworth-Emmons (HWE) olefination reaction in H_2O/2-propanol (1:1) and a convenient protocol to prepare AlH_3 in tetrahydrofuran from $LiAlH_4$ and *n*-butyl bromide are the key factors in the improvement.

Chapter 2 presents an asymmetric synthesis of D-*ribo*-phytosphingosine. The synthesis was achieved by utilizing the ProPhenol-catalyzed alkynylation of an

unsaturated aldehyde to afford an allylic propargylic alcohol followed by asymmetric epoxidation and opening of a propargylic epoxy alcohol with NaN_3/NH_4Cl. Deprotection and reduction of the resulting acyclic azide then gave D-*ribo*-phytosphingosine. The acyclic azide was also subjected to an intramolecular click reaction, generating a bicyclic triazole, whose diacetate derivative was found to have almost identical *cis* and *trans* vicinal coupling constants. The relative stereochemistry of the final product was assigned by NMR analysis of corresponding Mosher esters and amides, and confirmed by comparison of NMR spectra and specific rotations of its tetraacetate derivative with reported data. The stereochemical assignment based on comparing *J* values with reported data in bicyclic triazoles, generated by a copper-free intramolecular click reaction, was inconclusive. Alkynyl-azide, an efficient glycosyl acceptor in the synthesis of α-galactosylceramide derivatives, was also readily prepared by this route.

Chapter 3 presents (1) a modification of the first generation synthesis of α-1*C*-galactosylceramide featuring the two-step HWE olefination and alane reduction protocol described in Chapter 1 and the ProPhenol-catalyzed asymmetric alkynylation reaction, and (2) a detailed verification of the configurations of three contiguous stereogenic centers in the phytosphingosine moiety. Given the possible intramolecular participation by the 2'-*O*-benzyl group of the galactosyl moiety in epoxide opening by the azide anion, an attempt was made to assign the relative stereochemistry of the azide-bearing carbon through the coupling constants ($J_{4,5}$ and $J_{5,6}$) in a bicyclic triazole, which was obtained via an intramolecular click reaction and acetylation of diol. The *cis* $J_{4,5}$ and *trans* $J_{5,6}$ displayed almost the same values,

suggestive of possible retention in the opening of the epoxide; however, nOe analysis was inconclusive. Model compounds containing the same bicyclic triazole skeleton were prepared via the same reaction sequence, and their *cis* $J_{4,5}$ and *trans* $J_{5,6}$ coupling constants showed similar values as to those in the sugar counterpart. According to the systematical investigation of the model compounds described in Chapter 2, the epoxide-opening reaction did indeed proceed with inversion. These results exclude intramolecular participation by the 2'-*O*-benzyl group and emphasize the need for caution when coupling constants alone are used to judge the relative configuration in bicyclic triazoles and related systems.

Chapter 4 presents stereocontrolled syntheses of α-*C*-GalCer and its α-*C*-acetylenic analog from 1-hexadecene and D-galactose. The key transformations include Sonogashira coupling, Sharpless asymmetric epoxidation, and Et_2AlCl-catalyzed cyclization of an epoxytrichloroacetimidate to generate a protected dihydrooxazine synthon.

Dedication

Dedicated to those who made this thesis possible:

my parents, my wife

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I am sincerely grateful to my research mentor, Distinguished Professor Robert Bittman, for his professional guidance. He not only helped me in project design and development in my research work, but also took much time and energy to review all of my reports and papers and made valuable comments as well as corrections. I would also like to thank him for freedom that I was granted to pursue and explore new chemistries, as well as the encouragement and inspiration when I was confronted with difficulties. All of those will be my life-time treasure and endless strength in the future.

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Table of Contents

List of Schemes

List of Figures and Tables

Abbreviations

Å	Angstrom
aq	aqueous
$BF_3 \cdot OEt_2$	boron trifluoride diethyl etherate
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bz	benzoyl
^{13}C NMR	carbon-13 nuclear magnetic resonance
ca.	approximately
calcd	calculated
cat	catalytic
CD1	cluster of differentiation 1
CSA	camphorsulfonic acid
d	doublet
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
dd	doublet of doublets
de	diastereomeric excess
DIBAL-H	diisobutylaluminum hydride
DIPT	diisopropyl tartrate
DMAP	4-(dimethylamino)pyridine
ee	enantiomeric excess
eq or equiv	equivalent

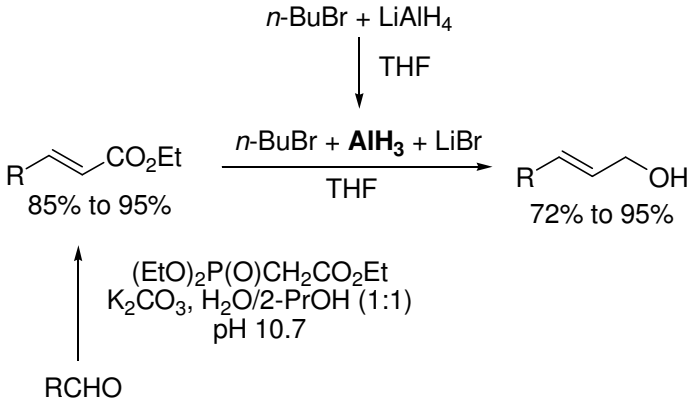
ESI	electrospray ionization
Gal	galactose
GSL	glycosphingolipid
^{1}H NMR	proton nuclear magnetic resonance
h	hour
HRMS	high-resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons
Hz	Hertz
IFN-γ	interferon-gamma
IL-2	interleukin-2
IL-4	interleukin-4
LAH	lithium aluminum hydride
min	minute
MS	molecular sieves
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetyl
NKT	natural killer T
NMR	nuclear magnetic resonance
PCC	pyridium chlorochromate
Pd/C	palladium on carbon
PMB	*p*-methoxybenzyl
2-PrOH	2-propanol
quant	quantitative
rt	room temperature

s	singlet
SAE	Sharpless asymmetric epoxidation
SAR	structure activity relationship
t	triplet
TBAF	tetra-*n*-butylammonium fluoride
TBAI	tetra-*n*-butylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBDPS	*tert*-butyldiphenylsilyl
Tf	triflate; trifluoromethanesulfonyl
TFA	trifluoroacetic acid
Tf_2O	trifluoromethanesulfonic anhydride
Th1	Type 1 helper
Th2	Type 2 helper 2
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMSCl	trimethylsilyl chloride
TMSOTf	trimethylsilyl trifluoromethanesulfonate
TsOH	*p*-toluenesulfonic acid

Chapter 1: An Improved Two-step Synthetic Route to Primary Allylic Alcohols from Aldehydes

1.1 Abstract

An improved two-step synthetic route to allylic alcohols from aldehydes has been developed. A modification of the HWE reaction in H_2O/2-PrOH (1:1) and a convenient protocol to prepare AlH_3 in THF from $LiAlH_4$ and *n*-butyl bromide are the key factors in the improvement.



1.2 Introduction

Allylic alcohols are important synthons in organic synthesis, and asymmetric epoxidation[1] of allylic alcohols is widely used at the chiral induction stage in many syntheses of natural products. Among the many ways to prepare allylic alcohols, an important two-step route is the Horner-Wadsworth-Emmons (HWE) addition of

dialkyl carboalkoxymethylenephosphonates to aldehydes to generate α,β-unsaturated esters which, in turn, are reduced to allylic alcohols by DIBAL-H.

Most generally, α,β-unsaturated esters are prepared by the HWE reaction,[3] which is classically carried out using a hydride or organometallic base in anhydrous aprotic solvents under an inert atmosphere. In nonpolar solvents the reaction of stablized ylides with aldehydes proceeds very slowly.[4] Moreover, the *E*/*Z* stereoselectivity, and thus the utility of the HWE reaction, is complicated by several factors, such as the nature of the metal counterion employed,[5] reaction temperature,[5] the size of the phosphonoester reagent used,[6] and the presence of oxygen-containing groups adjacent to the carbonyl group.[3c] Villieras et al.[7] reported the HWE reactions of triethyl phosphonoacetate with aldehydes in highly concentrated (6 to 10 M) aqueous solutions of K_2CO_3 or $KHCO_3$. Compared with the traditional HWE reaction, the aqueous HWE reaction has the following advantages:[8] (1) It can be used for large scale preparations; (2) wet aldehydes can be used directly in the reaciton as substrates; (3) water is believed to accelerate the reaction;[9] (4) it is environmentally friendly; (5) acid- and base-sensitive functional groups can survive under the reaction conditions; and (6) high *E*-selectivities can normally be achieved. However, as the introduction of water as the essential medium for performing the HWE reaction utilizing poorly water-soluble aldehydes is very limited, only isolated examples are known; therefore, phase-transfer catalysts[10] and high reaction temperatures[7] (up to 100 °C) are generally required.

For the reduction of α,β-unsaturated esters, DIBAL-H[11] is the preferred reagent because other reducing reagents such as LAH and $NaBH_4$[12] generally give low

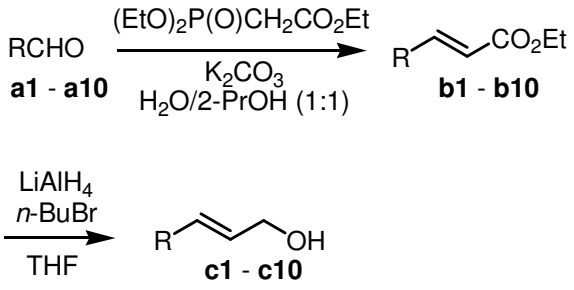
yields as a result of competing 1,2- and 1,4-addition reactions. Unfortunately, DIBAL-H reduction requires more than 2 equiv, and workup is tedious because it involves the use of a large volume of aqueous potassium sodium tartrate (Rochelle salt; Seignette salt) solution. Although AlH_3 also reduces α,β-unsaturated esters to allylic alcohols, and in some instances may be superior to both DIBAL-H and LAH,[13] its preparation is cumbersome. Thus DIBAL-H continues to be the reagent that is most commonly used.

Currently, there are three methods of preparation of AlH_3. First, it can be prepared by reaction of three equivalents of LAH with $AlCl_3$.[14] AlH_3 prepared in this way is not always pristine since a mixed chloroaluminum hydride species can be formed, depending on the proportions of LAH and $AlCl_3$.[15] In addition, $AlCl_3$ is hygroscopic and difficult to handle. Second, AlH_3 can be prepared by treating LAH with the theoretical quantity of 100% H_2SO_4 in THF.[16] This protocol is problematical because it is difficult to prepare a standardized LAH solution in THF and to control the addition of the theoretical quantity of the very viscous 100% H_2SO_4 into the LAH solution. Indeed, it was reported that addition of dilute H_2SO_4 to a solution of LAH in THF led to an explosion.[17] In a third method, a tertiary amine-alane adduct was utilized in the 1990's.[18] This procedure makes the preparation simpler but still requires the extraction of the amine-alane complex from LAH under an inert atmosphere. Brown et al.[19] reported in 1982 that AlH_3 is formed as a by-product of the reduction of an alkyl halide with LAH.[20] In 1994, we employed Brown's reaction to generate AlH_3 for an *in situ* reduction of ethyl α-(hydroxymethyl)acrylate to α-(hydroxymethyl)acrolein.[21] However, this mode of

AlH_3 preparation was little noted,[22] as evident from the continued use of 100% H_2SO_4 and LAH to generate AlH_3 in the total synthesis (±)-gelsemine by the Overman group.[23]

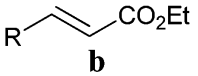
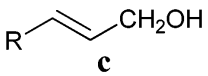
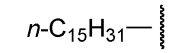
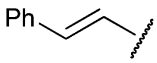
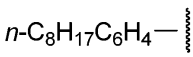
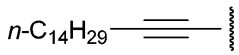
In this Chapter it is shown that the HWE reaction of a variety of aldehydes with triethyl phosphonoacetate in the presence of K_2CO_3 in H_2O/2-PrOH (1:1) produced (*E*)-α,β-unsaturated esters with convenience and efficiency. When 2-propanol and water were used as co-solvents, it was discovered that a broad spectrum of substrates can be used in the HWE reaction at room temperature with improved yields and without any detrimental effect on their high *E*-selectivities. This Chapter also reports an improved and convenient procedure for the preparation of AlH_3 and its *in situ* reduction of (*E*)-α,β-unsaturated esters. The combination of these two procedures provides an improved route to allylic alcohols from aldehydes, especially on a large scale (Scheme 1.1).

Scheme 1.1 HWE Reaction in H_2O/2-PrOH and Reduction of α,β-Unsaturated Esters by AlH_3



1.3 Results and Discussion

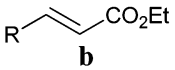
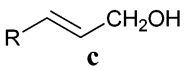
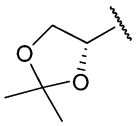
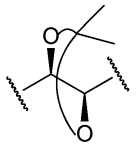
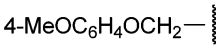
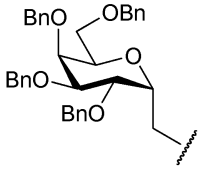
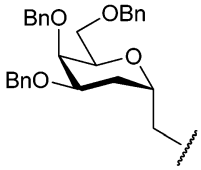
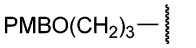
Table 1.1 HWE reactions of aromatic and aliphatic aldehydes (**a**) followed by AlH_3 reduction of the resulting α,β-unsaturated esters (**b**) to afford allylic alcohols (**c**).

Entry	RCHO **a**	 **b**	 **c**
		Yield[a] (%), *E* : *Z*[b]	Yield[a] (%)
1		**b1**	**c1**
	a1	92, 10 : 1	95
2		**b2**	**c2**
	a2	87, *E* only	83
3		**b3**	**c3**
	a3	95, *E* only	96
4		**b4**	**c4**
	a4	88, *E* only	87

[a] Isolated yields. [b] *E*/*Z* ratios were determined by ^{13}C NMR.

The reactions of **a1** - **a4** with triethyl phosphonoacetate furnished the corresponding (*E*)-α,β-unsaturated esters **b1** - **b4** in high yield and *E*-selectivity (Table 2.1). Wet heptadec-2-ynal (**a4**), obtained by formylation of 1-hexadecyne, can be subjected to this procedure directly without column chromatography to provide the corresponding enyne ester with predominant *E*-selectivity (entry 4). In comparison, a previous investigation[24] showed that the HWE reaction of hexadec-2-ynal with triethyl phosphonoacetate using LiBr and Et_3N[5b] proceeded with an *E*/*Z* ratio of 10:1 to 15:1 in the enyne ester, but the use of the sterically larger diisopropyl

Table 1.2 HWE reaction of aldehydes (**a**) with oxygen-containing groups adjacent to the carbonyl group, followed by AlH_3 reduction of the resulting α,β-unsaturated esters (**b**), to afford allylic alcohols (**c**).

Entry	RCHO **a**	 **b**	 **c**
		Yield[a] (%), E : Z[b]	Yield[a] (%)
1		**b5**	**c5**
	a5	85, 18 : 1	75
2		**b6**	**c6**
	a6	71, E only	72
3		**b7**	**c7**
	a7	86, 28 : 1	88
4		**b8**	**c8**
	a8	89, > 38 : 1	87
5		**b9**	**c9**
	a9	87, E only	85
6		**b10**	**c10**
	a10	85, 7 : 1	89

[a] Isolated yields. [b] E/Z ratios of entries 1–4 and 6 were determined by ^{13}C NMR; the E/Z ratio of entry 5 was determined by isolation of each compound.

(ethoxycarbonylmethyl)phosphonate in the reaction, as expected,[6] provided the *E* isomer exclusively.

To expand the scope of our modified HWE reaction, we also examined the conversion of aldehydes **a6** - **a10**, which bear oxygen-containing groups adjacent to the carbonyl group, to α,β-unsaturated esters **b6** - **b10** (Table 2.2). It has been reported[3c] that the reaction of this type of aldehyde with stabilized phosphonium ylides ($Ph_3P{=}CHCO_2R$) can result in abnormal reaction stereochemistry, and in certain cases furnish highly *Z*-rich acrylate mixtures. The aldehydes in entries 1-5 of Table 2.2 were prepared by oxidative cleavage of a vicinal diol with $NaIO_4$, followed by removal of the generated formaldehyde under reduced pressure without any further purification. Condensation of glyceraldehyde acetonide with triethyl phosphonoacetate afforded the (*E*)-conjugated ester **b5** as an 18/1 *E*/*Z* mixture (entry 1). A previous study showed that dialdehyde **a6** (entry 2) reacted with $Ph_3P{=}CHCO_2Me$ in methanol (-78 to 20 °C) to yield a mixture of diacrylates enriched in the *Z*,*Z* isomer (*Z*,*Z*/*Z*,*E*/*E*,*E* = ca. 12:10:1).[25] Chromatography on silica gel followed by crystallization in hexane can afford the pure *Z*,*Z* isomer of the corresponding dimethyl diacrylate as colorless crystals.[26] In contrast, it was found that the reaction of dialdehyde **a6** with the phosphonate in H_2O/2-PrOH followed by column chromatography on silica gel provided the *E*,*E* isomer **b6** in 71% yield (entry 2). The reaction with α-(*p*-methoxyphenoxy)-acetaldehyde (**a7**) provided the corresponding (*E*)-conjugated ester **b7** (entry 3), which was also prepared by a substitution reaction of alkyl 4-bromocrotonate with 4-methoxyphenol.[27] Significantly, this method is effective for the olefination of base-sensitive aldehydes,

probably because the reaction of triethyl phosphonoacetate with CO_3^{2-} in water produces a CO_3^{2-}-HCO_3^- buffer (pH 10.7). The aldehydes shown in entries 4 and 5 can undergo a base-induced anomerization via β-elimination followed by an intramolecular hetero-Michael reaction,[28] and thus can be contaminated by the β-epimer. To our delight, in the olefination reactions shown in entries 4 and 5, no β-anomer of the conjugated esters was observed. 4-(*p*-Methoxybenzyloxy)-butanal (**a10**) was prepared by 2,2,6,6-tetramethyl-1-piperdinyloxy (TEMPO) catalyzed oxidation of the corresponding alcohol with NCS[29] because it was found that partial deprotection of the *p*-methoxybenzyl group occurred during Swern oxidation of $PMBO(CH_2)_4OH$.[30] The resulting crude **a10** underwent the HWE reaction directly with moderate *E*-selectivity as well as eco-friendly character[29b] (entry 6).

The data in Tables 2.1 and 2.2 show that generation of AlH_3 in THF from LAH and *n*-BuBr[22] followed by *in situ* reduction of (*E*)-α,β-unsaturated esters **b1** - **b10** provides very high yields of allylic alcohols **c1** - **c10**. In comparison to the commonly used DIBAL-H-mediated reduction, this procedure has the following advantages, especially as far as scale-up is concerned: (1) α,β-unsaturated esters can be reduced with only 1.3 equiv of LAH;[31] (2) the workup procedure is very simple, involving quenching the reaction by addition of a stoichiometric quantity of 1 M NaOH solution or $Na_2SO_4 \cdot 10H_2O$ (~3 equiv of water based on LAH), followed by filtration through a pad of Celite.

Solvents may have a critical impact on the use of AlH_3. When AlH_3 is prepared by the reaction of LAH with $AlCl_3$ in Et_2O, a white precipitate is formed on standing overnight or longer, which, of course, results in a decrease in its

reducing capacity.[16a] In THF at reflux, a slow cleavage reaction takes place to give *n*-BuOH.[16a] For this reason, $AlH_2(OMe)$[32, 33] was prepared in toluene by the reaction of LAH with *n*-BuBr and $(CH_2O)_n$ at -78 °C. The yield of **c1** obtained by the $AlH_2(OMe)$-mediated reduction of **b1** in toluene was comparable to that found with AlH_3 in THF, indicating that $AlH_2(OMe)$ in toluene may be used for the 1,2-reduction of α,β-unsaturated esters to allylic alcohols when THF is not a suitable solvent.

1.4 Conclusion

The HWE reaction in H_2O/2-PrOH and the convenient preparation of AlH_3 provide easier access to primary allylic alcohols, which are valuable synthons in organic synthesis.

1.5 Experimental Section

Typical Procedure for Preparation of α,β-Unsaturated Ester by HWE Reaction in Water/2-PrOH: Preparation of b8.

To a solution of $NaIO_4$ (4.12 g, 19.2 mmol) in 100 mL of water were added $NaHCO_3$ (160 mg, 1.91 mmol) and then a solution of 3-(2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosyl)-1,2-propanediol (8.69 g, 14.5 mmol) in 100 mL THF at 0 °C. After the oxidative cleavage was completed (about 2 h at rt), the mixture was concentrated under reduced pressure to remove THF and the formaldehyde formed. The crude aldehyde **a8** was used directly in the HWE reaction without any further

purification. To a mixture of crude aldehyde **a8** and triethyl phosphonoacetate (4.68 g, 20.9 mmol) in 50 mL of 2-PrOH was added dropwise a solution of K_2CO_3 (26.0 g, 187 mmol) in 50 mL of water at 0 °C. The mixture was gradually warmed to rt and was stirred overnight at rt. The product was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The product was purified by column chromatography on silica gel (elution with hexane/EtOAc 10:1, 8:1, and 6:1) to give 8.23 g (89%) of ethyl 4-(2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosyl)-2(*E*)-butenoate (**b8**) together with 219 mg (2.4%) of its *Z* isomer (***Z*-b8**, which was contaminated with the *E* isomer) as colorless oils. **b8**[34]**:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (t, 3H, *J* = 7.1 Hz), 2.36-2.46 (m, 1H), 2.49-2.59 (m, 1H), 3.66 (dd, 1H, *J* = 4.6, 10.5 Hz), 3.69-3.75 (m, 2H), 3.79-3.87 (m, 1H), 3.97-4.01 (m, 1H), 4.01-4.09 (m, 2H), 4.14 (q, 2H, *J* = 7.1 Hz), 4.43-4.73 (m, 8H), 5.87 (d, 1H, *J* = 15.6 Hz), 6.91 (dt, 1H, *J* = 7.1, 15.6 Hz), 7.20-7.36 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 30.8, 60.1, 66.9, 70.0, 72.7, 73.05, 73.09, 73.2, 74.0, 76.3, 123.2, 127.4, 127.50, 127.54, 127.61, 127.72, 127.79, 127.81, 127.9, 128.25, 128.27, 128.31, 128.34, 137.9, 138.24, 138.28, 138.33, 145.4, 166.3. HRMS (ESI) ($M+NH_4^+$) $C_{40}H_{48}NO_7$ calcd for *m/z* 654.3425, found 654.3427. ***Z*-b8:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.87-2.97 (m, 1H), 3.14-3.27 (m, 1H), 3.51-3.64 (m, 1H), 3.72-3.79 (m, 2H), 3.84-3.92 (m, 1H), 3.97-4.01 (m, 1H), 4.02-4.07 (m, 2H), 4.41-4.81 (m, 8H), 5.83 (d, *J* = 11.5 Hz, 1H), 6.28 (dt, *J* = 11.5, 7.1 Hz, 1H), 7.19-7.41 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 59.8, 67.7, 72.0, 73.0, 73.1, 73.2, 73.4, 73.5, 74.3, 120.9, 127.41, 127.49, 127.56,

127.60, 127.8, 127.9, 128.1, 128.20, 128.24, 128.28, 128.31, 128.39, 138.30, 138.32, 138.45, 138.55, 147.1, 166.4.

Typical Procedure for AlH_3 Reduction of an α,β-Unsaturated Ester in THF: Preparation of c8.

To a mixture of LAH (700 mg, 18.4 mmol, 95% fine powder) in 100 mL of THF was added *n*-BuBr (2.0 mL, 18.5 mmol) at -78 °C. The reaction mixture was warmed to rt and stirred overnight. To the mixture was added a solution of **b8** (7.96 g, 12.5 mmol) in 50 mL of THF at -78 °C. After being stirred for 2 h, the mixture was gradually warmed to rt. After all of the starting ester was consumed (about 2 h at rt), the reaction was quenched by addition of 2 mL of 1 M NaOH solution. The mixture was diluted with 150 mL of CH_2Cl_2 and passed through a pad of Celite, which was washed with 250 mL of EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (elution with hexane/EtOAc 2:1 and 1:1) to give 6.47 g (87%) of 4-(2',3',4',6'-tetra-*O*-benzyl-α-D-galactopyranosyl)-2(*E*)-buten-1-ol (**c8**)[34] as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71 (br s, 1H), 2.25-2.35 (m, 1H), 2.35-2.45 (m, 1H), 3.60 (dd, 1H, *J* = 4.2, 10.5 Hz), 3.69-3.78 (m, 2H), 3.79-3.88 (m, 1H), 3.91-4.07 (m, 5H), 4.43-4.73 (m, 8H), 5.53-5.69 (m, 2H), 7.22-7.35 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.5, 63.4, 67.4, 70.7, 72.3, 72.90, 72.96, 73.02, 73.08, 74.2, 76.3, 76.4, 127.39, 127.46, 127.51, 127.53, 127.7, 127.81, 127.85, 128.19, 128.26, 128.8, 131.3, 138.10, 138.17, 138.29, 138.5.

Procedure for Reduction of α,β-Unsaturated Ester b1 with $AlH_2(OMe)$ in Toluene: Preparation of c1.

To a suspension of LAH (2.10 g, 55.3 mmol, 95% fine powder) in 100 mL of toluene were added *n*-BuBr (6.0 mL, 55.9 mmol) and, after 2 h, paraformaldehyde (1.66 g, 55.3 mmol) at -78 °C. The mixture was gradually warmed to rt and stirred overnight. To this $AlH_2(OMe)$ mixture was added dropwise a solution of **b1** (13.2 g, 42.5 mmol) in 100 mL of toluene at 0 °C. After the mixture was gradually warmed to rt and stirred overnight, it was diluted with 50 mL of dry THF[35] and stirred for 10 min. The reaction was quenched by addition of 6 mL of 1 M NaOH solution, and the mixture was diluted with 100 mL of CH_2Cl_2. The mixture was passed through a pad of Celite, which was rinsed with EtOAc. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (elution with hexane/EtOAc 6:1) to give 9.82 g (86%) of 2(*E*)-octadecen-1-ol (**c1**).

(*E*)-Ethyl Octadec-2-enoate (b1)

Matches the published data.[36]

(*E*)-Octadec-2-en-1-ol (c1)

Matches the published data.[37] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.26 (s, 26H), 1.34-1.39 (m, 2H), 1.56 (s, 1H), 2.04 (q, 2H, J = 7.2 Hz), 4.09 (t, 2H, J = 5.2 Hz), 5.61-5.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 29.1, 29.2, 29.4, 29.5, 29.60, 29.65, 29.68, 31.9, 32.2, 63.8, 128.7, 133.6.

(2*E*,4*E*)-Ethyl 5-Phenylpenta-2,4-dienoate (b2)

Matches the published data.[38]

(2*E*,4*E*)-5-Phenylpenta-2,4-dien-1-ol (c2)

Matches the published data.[39]

(*E*)-Ethyl 3-(4-Octylphenyl)acrylate (b3)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.16-1.38 (m, 13H), 1.53-1.65 (m, 2H), 2.61 (t, *J* = 2.6 Hz, 2H), 4.26 (q, *J* = 7.1 Hz, 2H), 6.39 (d, *J* = 16.0 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.67 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.3, 22.6, 29.21, 29.26, 29.4, 31.2, 31.8, 35.8, 60.4, 117.1, 128.0, 128.9, 131.9, 144.6, 145.7, 167.2.

(*E*)-3-(4-Octylphenyl)prop-2-en-1-ol (c3)

^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.21-1.36 (m, 10H), 1.44 (t, 4.9, 1H), 1.55-1.64 (m, 2H), 2.58 (t, *J* = 7.8 Hz, 2H), 4.31 (t, *J* = 4.8 Hz, 2H), 6.32 (dt, *J* = 15.9, 5.9 Hz, 1H), 6.59 (d, *J* = 15.9 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 2H), 7.30 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 29.28, 29.33, 29.5, 31.5, 31.9, 35.7, 63.9, 126.4, 127.4, 126.7, 131.3, 134.0, 142.7.

(*E*)-Ethyl 6-(4-Methoxybenzyloxy)hex-2-enoate (b10)

Matches the published data.[29b]

(*E*)-6-(4-Methoxybenzyloxy)hex-2-en-1-ol (c10)

Matches the published data.[40]

(*E*)-Ethyl Nonadec-2-en-4-ynoate (b4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.19-1.45 (m, 25H), 1.50-1.60 (m, 2H), 2.36 (dt, *J* = 2.2, 7.1 Hz, 2H), 4.20 (q, *J* = 7.1 Hz, 2H), 6.13 (d, *J* = 15.8 Hz, 1H), 6.76 (dt, *J* = 15.8, 2.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 14.2, 19.7, 22.7, 28.3, 28.8, 29.1, 29.3, 29.5, 29.58, 29.62, 29.65, 29.67, 31.9, 60.5, 77.9, 100.8, 126.1, 129.2, 166.1.

(*E*)-Nonadec-2-en-4-yn-1-ol (c4)

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.18-1.45 (m, 23H), 1.47-1.57 (m, 2H), 2.29 (dt, *J* = 1.9, 7.0 Hz, 2H), 4.18 (t, *J* = 4.7 Hz, 2H), 5.72 (dt, *J* = 15.9, 1.9 Hz, 1H), 6.16 (dt, *J* = 15.9, 5.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.4, 22.7, 28.7, 28.9, 29.1, 29.4, 29.5, 29.62, 29.65, 29.67, 29.69, 31.9, 63.1, 78.2, 91.5, 111.4, 140.1.

(*E*)-Ethyl 3-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]acrylate (b5)[41]

^{1}H NMR (400 MHz, C_6D_6) δ 0.98 (t, *J* = 7.1 Hz, 3H), 1.24 (s, 3H), 1.28 (s, 3H), 3.25-3.30 (m, 1H), 3.66-3.71 (m, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 4.20-4.27 (m, 1H), 6.13 (dd, *J* = 15.6, 1.5 Hz, 1H), 6.85 (dd, *J* = 15.6, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 14.2, 25.8, 26.5, 60.3, 68.8, 75.1, 110.0, 122.2, 145.2, 165.7.

(*E*)-3-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl]prop-2-en-1-ol (c5)[41]

^{1}H NMR (500 MHz, C_6D_6) δ 1.36 (s, 3H), 1.42 (s, 3H), 3.41 (t, *J* = 7.8 Hz, 1H), 3.73-3.83 (m, 3H), 4.31 (q, *J* = 6.9 Hz, 1H), 5.55 (dd, *J* = 15.5, 6.7 Hz, 1H), 5.63 (dt, *J* = 15.5, 4.7 Hz, 1H); ^{13}C NMR (100 MHz, C_6D_6) δ 26.1, 26.9, 62.1, 69.5, 76.9, 109.4, 128.2, 133.7.

(*E*)-Ethyl 4-(4-Methoxyphenoxy)but-2-enoate (b7)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, *J* = 7.1 Hz, 3H), 1.71-1.79 (m, 2H), 2.25-2.33 (m, 2H), 3.45 (t, *J* = 6.3 Hz, 2H), 3.79 (s, 3H), 4.17 (q, *J* = 7.1 Hz, 2H), 4.42 (s, 2H), 5.82 (dt, *J* = 15.7, 1.6 Hz, 1H), 6.85-6.89 (m, 2H), 6.96 (dt, *J* = 15.7, 6.9 Hz, 1H), 7.22-7.27 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 28.0, 28.8, 55.1, 60.2, 68.8, 72.5, 113.6, 121.5, 129.1, 130.3, 148.5, 159.1, 166.5.

(*E*)-4-(4-Methoxyphenoxy)but-2-en-1-ol (c7)

Matches the published data.[27]

(4*R*,5*R*)-4,5-*O*-Isopropylidene-4,5-dihydroxy-2,6-octadiene-dioate (b6)[42]

^{1}H NMR (400 MHz, C_6D_6) δ 0.98 (t, *J* = 7.1 Hz, 6H), 1.25 (s, 6H), 3.95-4.04 (m, 6H), 6.12 (d, *J* = 15.6 Hz, 2H), 6.85 (ddd, *J* = 15.6, 1.8, 3.5 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 14.6, 27.1, 60.8, 80.2, 110.9, 124.0, 142.9, 165.7.

3-[(4*R*,5*R*)-5-(3-Hydroxy-1-(*E*)-propen-1-yl)-2,2-dimethyl-[1,3]dioxolan-4-yl]-prop-2-(*E*)-en-1-ol (c6)[43]

^{1}H NMR (400 MHz, C_6D_6) δ 1.47 (s, 6H), 2.83 (br s, OH, 2H), 3.94 (d, *J* = 4.8 Hz, 4H), 4.16-4.21 (m, 2H), 5.73 (ddd, *J* = 15.5, 4.8, 1.8 Hz, 2H), 5.90 (dt, *J* = 15.5, 4.8 Hz, 2H); ^{13}C NMR (100 MHz, C_6D_6) δ 27.3, 62.4, 82.0, 109.1, 126.8, 134.4.

4-(2'-Deoxy-3',4',6'-tri-*O*-benzyl-α-D-galactopyranosyl)-2(*E*)-butenoate (b9)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.1 Hz, 3H), 1.47-1.55 (m, 1H), 1.98-2.06 (m, 1H), 2.25-2.33 (m, 1H), 2.41-2.50 (m, 1H), 3.68-3.73 (m, 1H), 3.73-3.76 (m, 1H), 3.78-3.83 (m, 1H), 3.90-3.98 (m, 1H), 4.00-4.11 (m, 2H), 4.16(q, *J* = 7.1 Hz, 2H), 4.50-4.72 (m, 6H), 5.86 (d, *J* = 15.7 Hz, 1H), 6.91 (dt, *J* = 15.7, 7.2 Hz, 1H), 7.24-7.37 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 32.6, 36.3, 60.1, 66.6, 67.3, 71.4, 72.2, 73.11, 73.14, 73.6, 74.9, 123.4, 127.2, 127.41, 127.43, 127.5, 127.6, 127.7, 128.22, 128.26, 138.28, 138.36, 138.46, 144.7, 166.2. ESI-HRMS $[M+NH_4]^+$ calcd for *m/z* $C_{33}H_{42}NO_6^+$ 548.3007, found 548.3002.

4-(2'-Deoxy-3',4',6'-tri-*O*-benzyl-α-D-galactopyranosyl)-2(*E*)-buten-1-ol (c9)

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47-1.56 (m, 1H), 1.99-2.08 (m, 1H), 2.10-2.19 (m, 1H), 2.28-2.38 (m, 1H), 3.63-3.69 (m, 2H), 3.72-3.76 (m, 1H), 3.78-3.83 (m,

1H), 3.88-3.95 (m, 1H), 3.96-4.00 (m, 1H), 4.01-4.07 (m, 2H), 4.47-4.74 (m, 6H), 5.61-5.67 (m, 2H), 7.20-7.40 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0, 36.1, 63.4, 67.9, 71.2, 72.4, 73.1, 73.2, 73.5, 74.9, 127.3, 127.4, 127.5, 127.8, 128.24, 128.29, 128.34, 128.6, 138.3, 138.4, 138.6. ESI-HRMS $[M+NH_4]^+$ calcd for *m/z* $C_{31}H_{40}NO_5$ 506.2901, found 506.2899.

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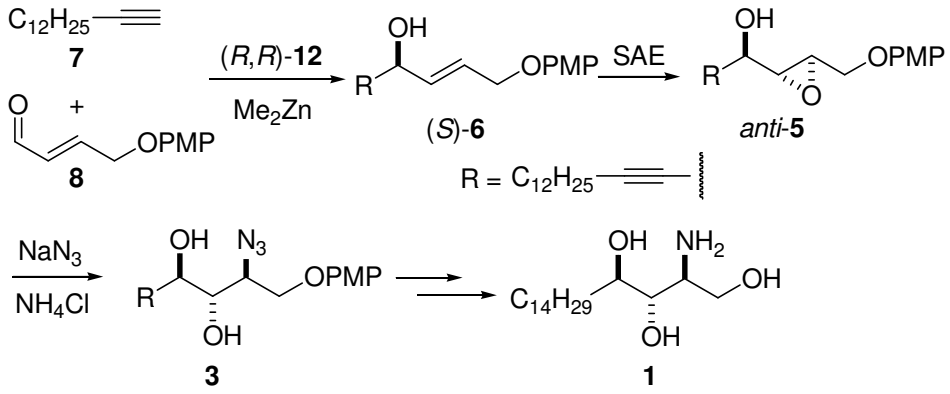
(42) Alexakis, A.; Tomassini, A.; Leconte, S. *Tetrahedron* **2004**, *60*, 9479. ^1H and ^{13}C NMR data in $CDCl_3$ were reported.

(43) Barros, M. T.; Charmier, M. A. J.; Maycock, C. D.; Michaud, T. *Tetrahedron* **2005**, *61*, 7960. ^1H and ^{13}C NMR data in $CDCl_3$ were reported.

Chapter 2: Asymmetric Synthesis of D-*ribo*-Phytosphingosine from 1-Tetradecyne and (4-Methoxyphenoxy)acetaldehyde

2.1 Abstract

An asymmetric synthesis of D-*ribo*-phytosphingosine (**1**) was achieved by utilizing the ProPhenol-catalyzed alkynylation of α,β-unsaturated aldehyde **8** to afford allylic propargylic alcohol (*S*)-**6** followed by asymmetric epoxidation and opening of propargylic epoxy alcohol **5a** with NaN_3/NH_4Cl. Deprotection and reduction of the resulting acyclic azide **3** then gave **1**. The acyclic azide **3** was subjected to an intramolecular click reaction, generating bicyclic triazole **14**, whose



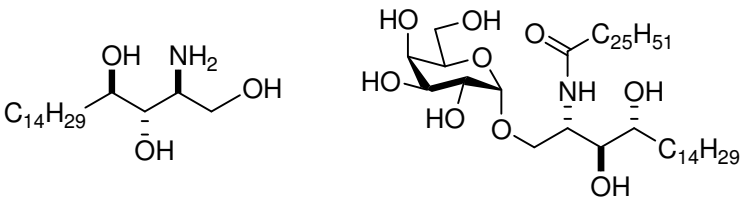
diacetate derivative **15a** was found to have almost identical *cis* and *trans* vicinal coupling constants. The relative stereochemistry of final product **1** was assigned by NMR analysis of the corresponding MTPA esters and amides, and confirmed by comparison of NMR spectra and specific rotations of **1** and its tetraacetate derivative **23** with reported data. Stereochemical assignment by comparing *J* values with

reported data in bicyclic triazoles **15a** and **15b**, generated by a copper-free intramolecular click reaction of **3**, was inconclusive. Alkynyl-azide **4**, an efficient glycosyl acceptor in the synthesis of α-galactosylceramide derivatives, was also readily prepared by this route.

2.2 Introduction

2*S*,3*S*,4*R*-(D-*ribo*)-Phytosphingosine (4D-hydroxysphinganine, PHS, **1**, Figure 2.1) is distributed ubiquitously, including in membranes of fungi, plants, bacteria, marine organisms, and mammalian tissues.[1] In addition to its structural role in membranes, **1** regulates cellular growth[2] and mediates the heat stress response of yeast.[3] Moreover, **1** serves as a metabolic precursor of important lipid mediators such as PHS 1-phosphate,[3b,4] inositol phosphorylceramide,[5] and KRN7000 (**2**, a naturally occurring α-galactosylceramide, and an immunostimulant of invariant natural killer T (iNKT) cells).[6]

Figure 2.1 Structures of D-*ribo*-phytosphingosine and α-galactosylceramide (KRN7000)



1
D-*ribo*-phytosphingosine

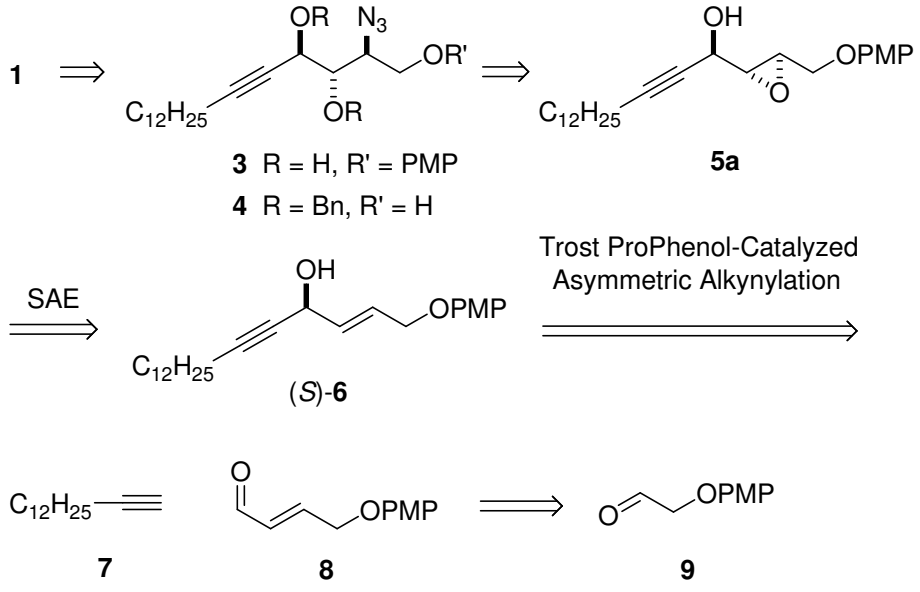
2
α-galactosylceramide (KRN7000)

Because of the biological importance of PHS, there has been considerable interest in the synthesis of **1** and its stereoisomers.[7] The construction of the three contiguous stereogenic centers poses an interesting and demanding challenge. Historically, natural chiral pools have played a significant role in their syntheses, but asymmetric reactions have emerged as a more favorable strategy for reasons of chirality economy and efficiency. Recently, the catalytic asymmetric alkynylation reaction developed by Trost et al. has been used as a key step in the syntheses of natural products.[8] As an extension of our previous studies on the synthesis of phytosphingolipids[7a,7c,9] and of glycolipid-based iNKT cell agonists,[10] we describe here a stereocontrolled synthesis of **1** via a sequence of catalytic alkynylation and Sharpless asymmetric epoxidation (SAE)[11] reactions to generate the intermediate chiral propargylic epoxy alcohol **5a** which was converted to **3** by ring-opening attack by azide ion. Although the ring opening was expected to result in an inversion of configuration at C-2, the stereochemical outcome required verification because of the report by Franck and co-workers of unexpected retention of configuration during a $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$-mediated epoxide ring-opening reaction.[12] To determine the relative configurations in azido diol **3**, we used an intramolecular click reaction[13] to form rigid bicyclic triazole **15a**, which, however, proved to have almost identical *cis* and *trans* vicinal coupling constants. Therefore, the determination of relative stereochemistry of **3** by coupling constants in **15a** was inconclusive. The configurations of the three contiguous stereogenic centers of **1** were instead determined by application of the advanced Mosher method.[14]

Interestingly, 2-azido alcohols have been found to be more favorable glycosyl acceptors than the corresponding 2-amido alcohols (ceramides).[15,16] Azido-alkynyl alcohol **4** was readily obtained by the synthetic procedure described here. Thus the route to **1** described herein may be used to prepare a glycosyl acceptor for the preparation of **2** and other galactosylceramide derivatives.[6,17]

2.3 Results and Discussion

Scheme 2.1 Retrosynthetic Plan



Outline of the Synthetic Plan. As illustrated in Scheme 2.1, we envisaged **1** and **4** to be accessible from azido diol **3**. The 2*S*,3*S* configuration in **3** can be generated by SAE on (*S*)-**6** followed by opening of the resulting epoxy alcohol **5a**

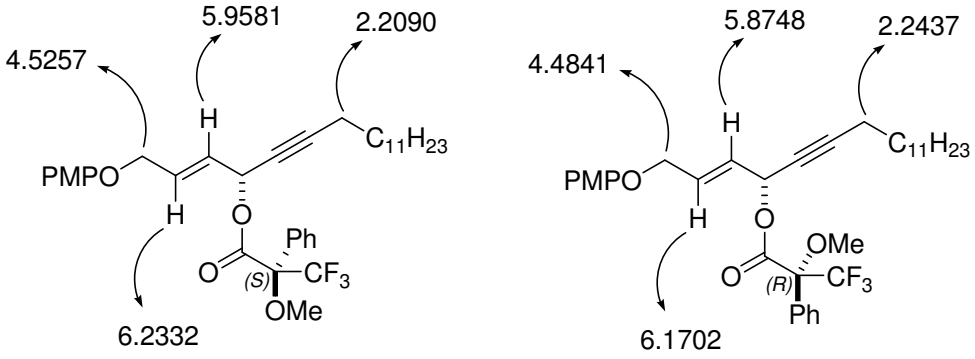
with NaN_3/NH_4Cl. Normally, SAE of (*S*)-**6** under kinetic resolution conditions can provide **5a** in high *ee* and *de*, even if the *ee* of (*S*)-**6** is not high. However, the *ee* of (*S*)-**6** plays a key role in maximizing the yield of **5a** in SAE. Indeed, (*S*)-**6** might be obtained in high *ee* via catalytic alkynylation of enal **8** with alkyne **7**. Asymmetric alkynylation of α,β-unsaturated aldehydes has been used in the synthesis of many complicated molecules with high efficiency,[18] but often requires stoichiometric or catalytic titanium in addition to zinc. Trost and co-workers have recently simplified and expanded the scope of this reaction.[8a] We have employed the Trost protocol to make **6** starting with enal **8**, which was prepared from commercially available aldehyde **9** using the two-step HWE/AlH_3 reduction protocol described in Chapter 1.[19] This synthetic route may permit access to other stereoisomers of **1** by using enantiomeric ligands in the catalytic alkynylation and SAE reactions.

Asymmetric Synthesis of Enynol (*S*)-6. On the basis of the retrosynthetic analysis depicted in Scheme 2.1, the first target, the conjugated (*E*)-enynol (*S*)-**6**, can be prepared by coupling of enal **8** with **7** by catalytic alkynylation. As shown in Scheme 2.2, allylic alcohol **11** was prepared from (4-methoxyphenoxy)-acetaldehyde (**9**)[20] via the two-step HWE/reduction protocol.[19] Previously, because it is difficult to achieve high *E*-selectivity by the HWE olefination reaction, (*E*)-α,β-unsaturated ester **10** was obtained by nucleophilic substitution of alkyl 4-bromocrotonate with 4-methoxyphenol.[21] HWE reaction of aldehyde **9** with triethyl phosphonoacetate in the presence of K_2CO_3 in H_2O/2-PrOH (1:1) produced ester **10** in 86% yield and high *E*-selectivity (*E*/*Z* = 28:1). Reduction with AlH_3 (generated from LAH and *n*-BuBr in THF),[19] followed by in situ reduction of ester **10**, provided

allylic alcohol **11** in 88% yield. Oxidation of allyl alcohol **11** with PCC gave (*E*)-α,β-unsaturated enal **8** in 58% yield.

The allylic propargylic alcohols with high *ee* have been accessible either by reduction of the corresponding ketone with a stoichiometric amount of pinanyl-borane[22] or by lipase-catalyzed resolution of racemic allylic propargylic alcohols.[23] In our hands, alkynylation of enal **8** with 1-tetradecyne catalyzed by ProPhenol ligand (*R*,*R*)-**12**[24] reproducibly provided a high yield of the desired (*E*)-enynol (*S*)-**6** (86%), but the enantiomeric excess was only moderate at best (60% ee). Under degassed reaction conditions, the chemical yield was improved, but the enantioselectivity was not. However, to our surprise, the alkynylation reaction catalyzed by ProPhenol ligand (*S*,*S*)-**12** provided *E*-enynol (*R*)-**6** with a high enantioselectivity (85% ee).[25] The *ee* value and absolute configuration of *E*-enynols (*S*)-**6** and (*R*)-**6** were determined by preparing the (*R*)- and (*S*)-MTPA esters and analyzing their ^{1}H-NMR spectra by the subtraction protocol of the advanced Mosher method. (Figures 2.2 and 2.3)[14]

Figure 2.2 MTPA ester chemical shifts for determination of absolute configuration of (*R*)-**6**



(*S*)-MTPA of **(*R*)-6** (*R*)-MTPA of **(*R*)-6**

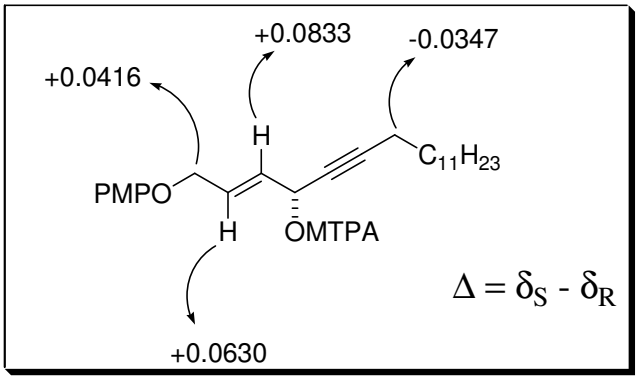
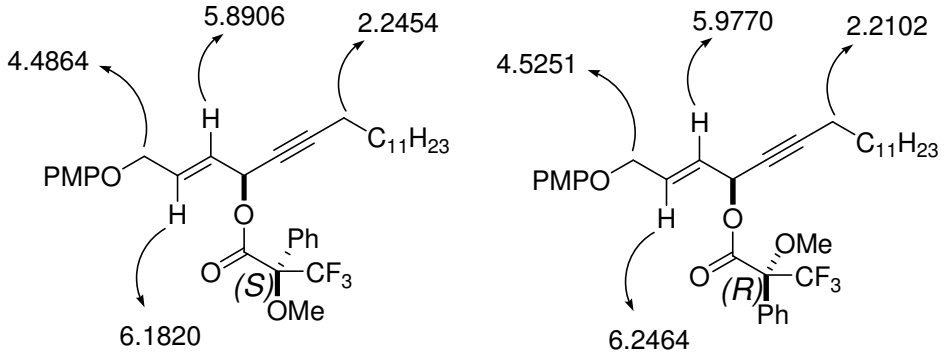
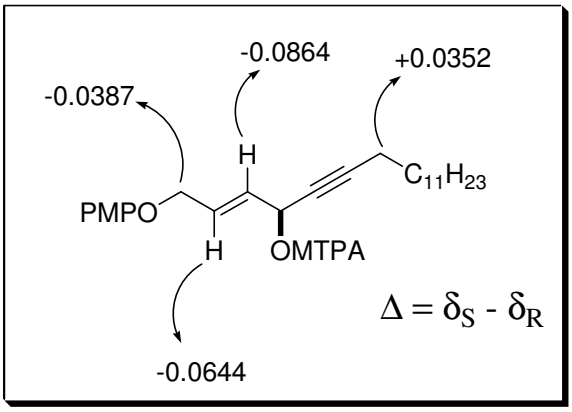


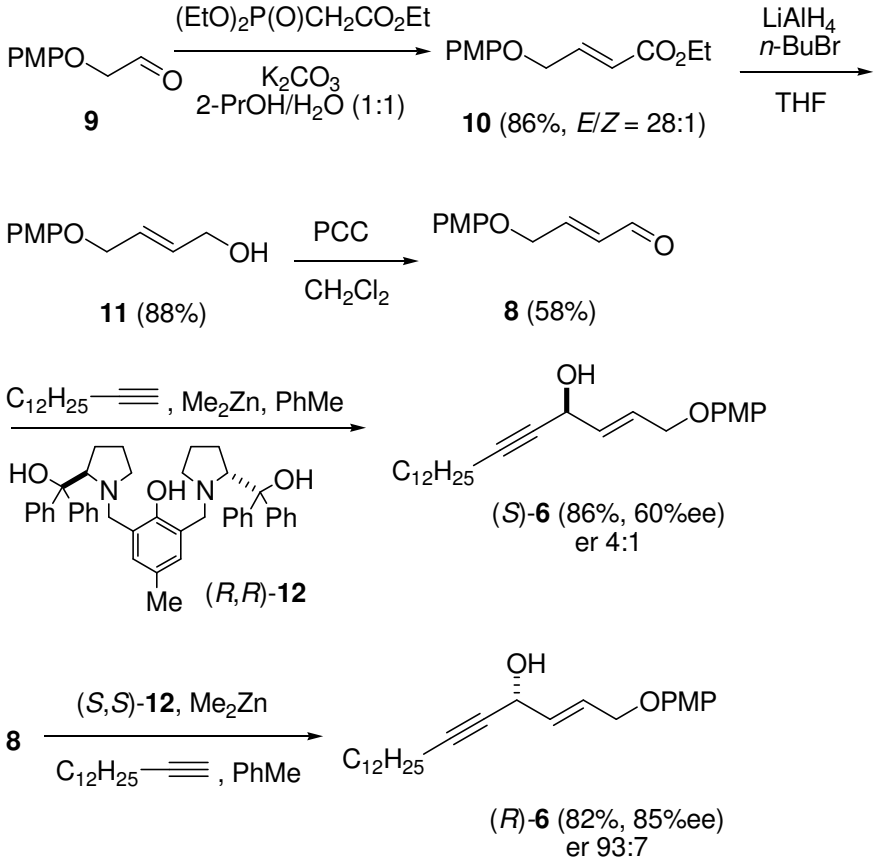
Figure 2.3 MTPA ester chemical shifts for determination of absolute configuration of (*S*)-**6**



(*S*)-MTPA of **(*S*)-6** (*R*)-MTPA of **(*S*)-6**



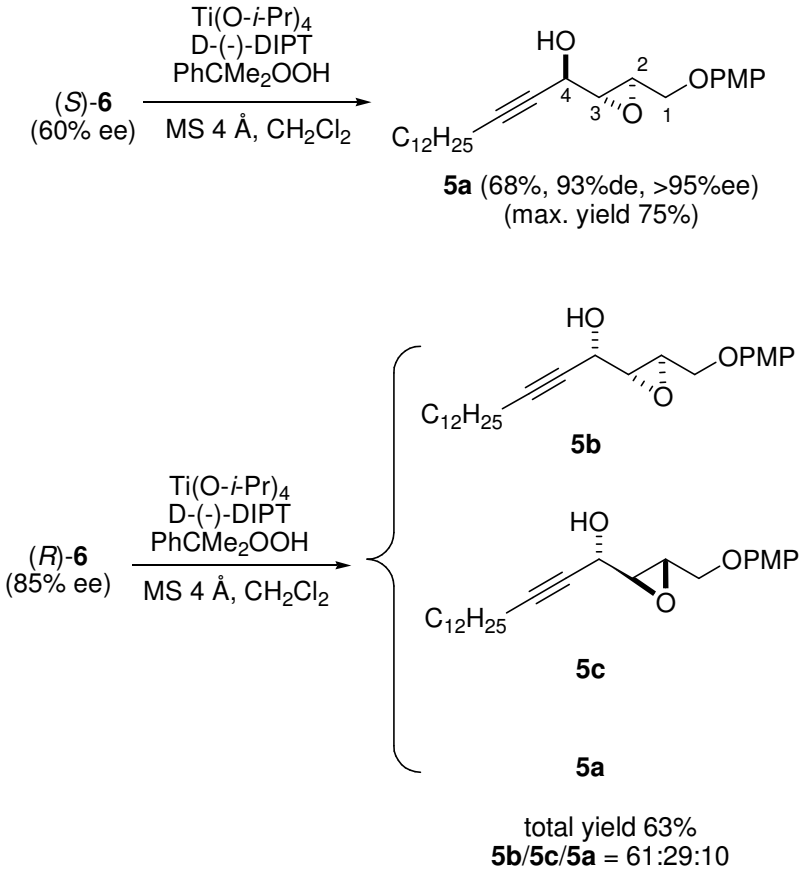
Scheme 2.2 Synthesis of Allylic Propargylic Alcohols (*S*)-**6** and (*R*)-**6**



Epoxidation of *E*-Enynol 6. As shown in Schemes 2.1 and 2.3, we intended to use SAE as one of the key steps to build the other two stereogenic centers from enynols (*S*)- and (*R*)-**6**. Under Sharpless kinetic resolution conditions, epoxidation of (*S*)-**6** (60% ee) with cumene hydroperoxide (CHP) in the presence of substoichiometric amounts of catalysts (D-(-)-DIPT, Ti(O-*i*-Pr-)$_4$) and 4Å molecular sieves gave epoxy alcohol **5a** in good yield (68%; the maximum theoretical yield based on the *ee* of (*S*)-**6** was 75%). After the unreacted substrate was removed by chromatography, the desired propargylic epoxy alcohol **5a** was obtained in high *de* (93%) and *ee* (>95%). In contrast, epoxidation of (*R*)-**6** (85% ee) under the same conditions led to **5a**, **5b**, and **5c**

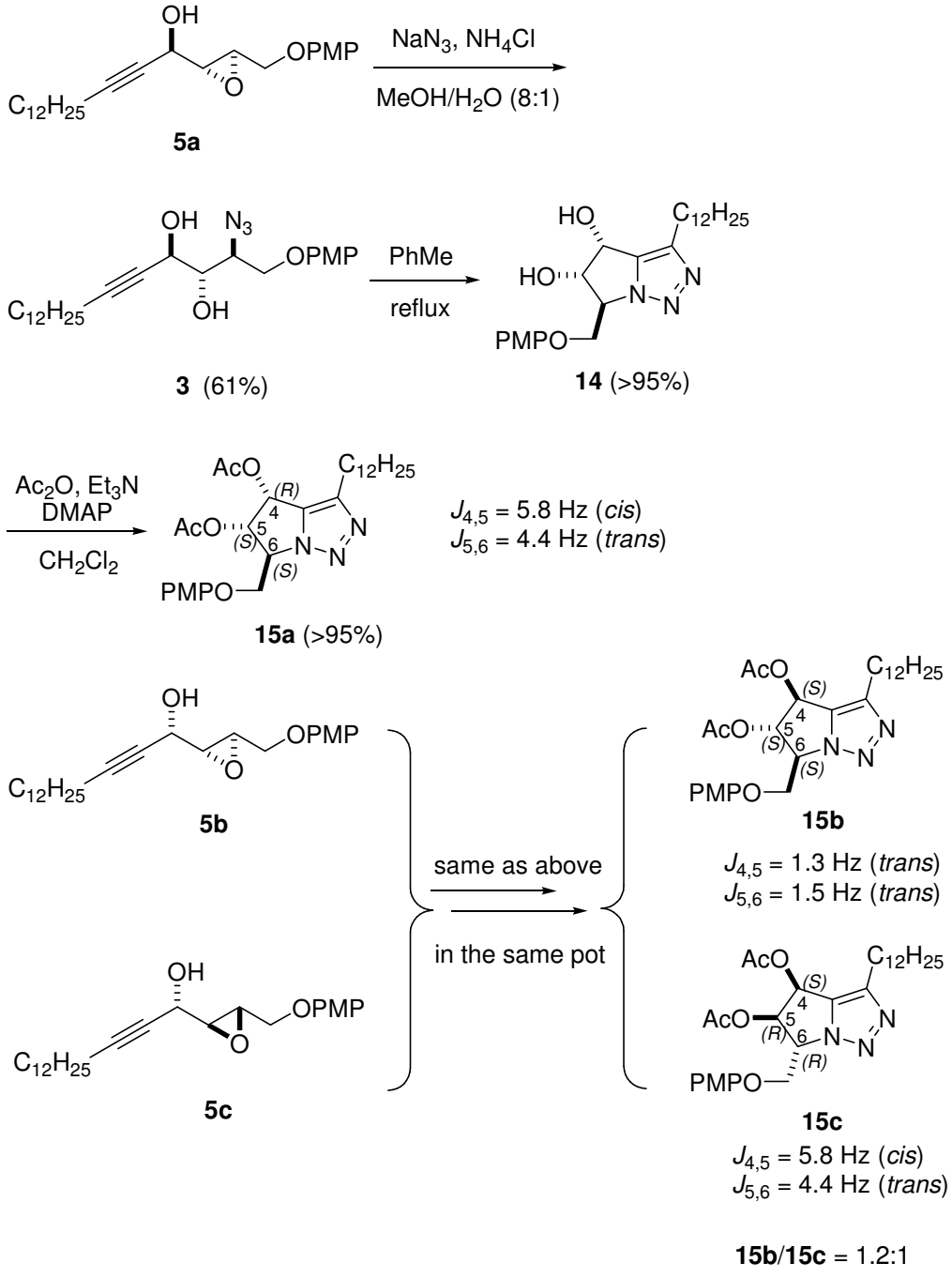
in a ratio of 10:61:29, indicating that the *R* configuration eroded the diastereomeric induction dominated by the catalyst.

Scheme 2.3 Synthesis of Epoxy Alcohols **5a** and **5b**



Opening of Epoxy Alcohol 5a. As shown in Scheme 2.4, opening of epoxy alcohol **5a** with NaN_3/NH_4Cl[26] provided azido diol **3** in 61% yield, together with other unidentified compounds. Although this reaction was not very clean, alternative methods, such as $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$,[27] were not attempted because in our prior experience this reagent gave rise to many unidentified compounds,[10,28]

Scheme 2.4 Opening of **5a**, **5b**, and **5c** and Coupling Constants in Bicyclic Triazole Derivative **15a**, **15b**, and **15c**

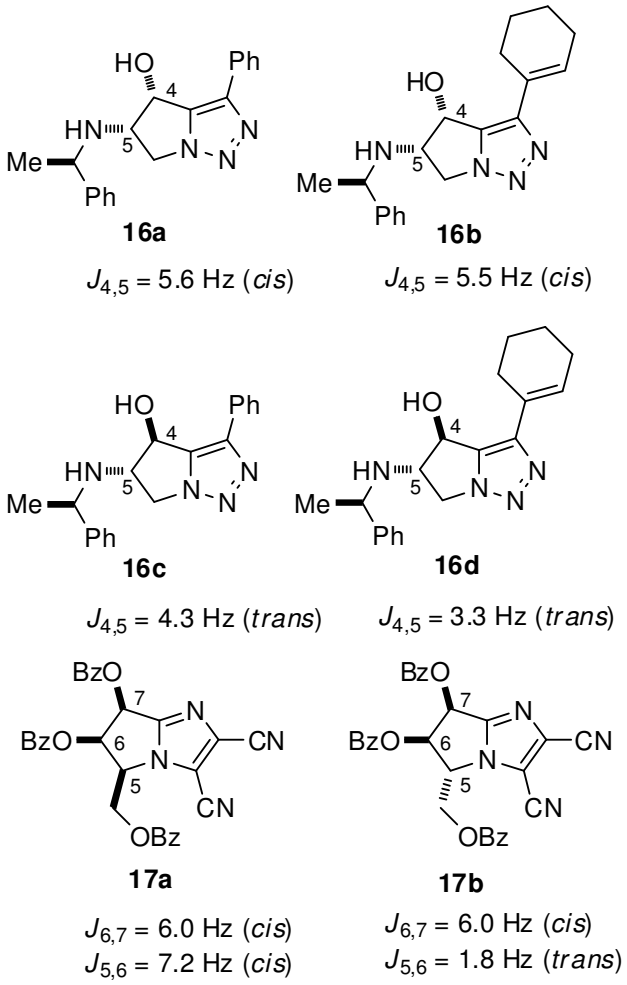


including the Ti-catalyzed semi-pinacol rearrangement product of α-hydroxy epoxides.[29]

Investigation of the Stereochemistry of the Azido Diols from 5a and 5b Based on *J* Values of Bicyclic Derivatives. To verify the stereochemistry of azido diols **3**, propargylic epoxy alcohol **5a** was converted to bicyclic dihydroxyl triazole **14** via a copper-free intramolecular click reaction in refluxing toluene for 48 h (Scheme 2.4).[13] **14** was then converted to diacetate **15a**. When **5b** and **5c** (inseparable) was subjected to the same reaction sequence, we obtained a mixture of diastereoisomer **15b** [4*S*,5*S*,6*S*] and **15c** ([4*S*,5*R*,6*R*], the enantiomer of **15a**) in a ratio of 1.2:1 (Scheme 2.4). The partial ^{1}H-NMR spectra of triazoles **15a**, **15b**, and **15c** are reported in Figure 2.5.

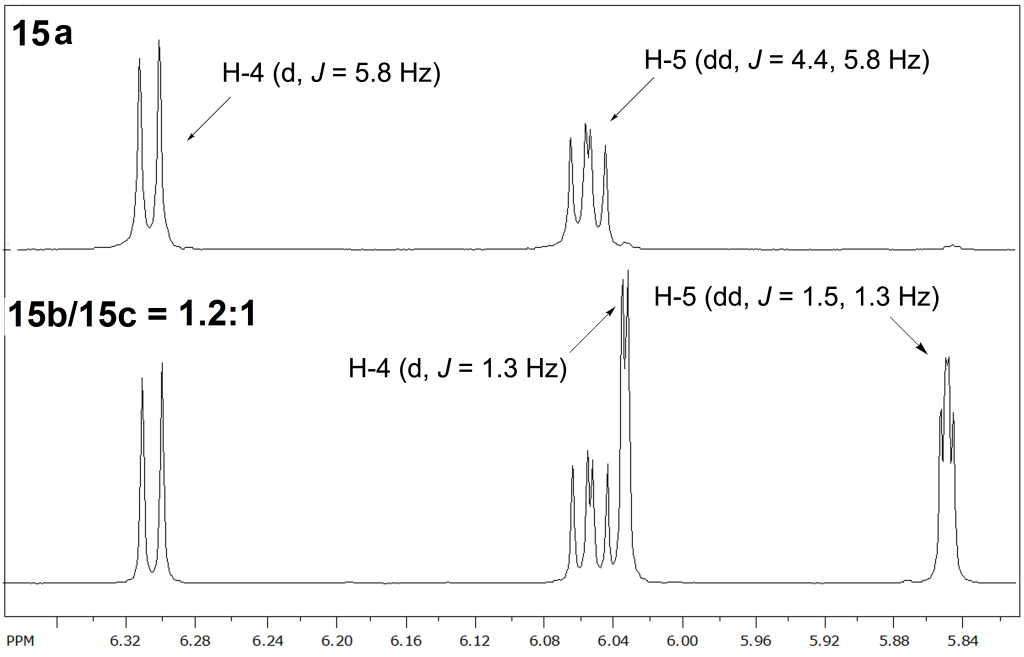
In 2005, Kim et al. prepared bicyclic triazoles **16a**-**16d** from chiral aziridines (Figure 2.4).[30a] The coupling constant in the *cis* relationship is 5.5-5.6 Hz, whereas that in the *trans* isomer is 3.3-4.3 Hz. Although H-4 in diol **14** gave a doublet signal (J = 5.5 Hz) and H-6 gave a quartet signal (J = 3.4 Hz), H-5 demonstrated an abnormal doublet of doublets (4.3 Hz and 5.0 Hz), probably because of intramolecular hydrogen bonding between the hydroxy and amino groups. The coupling constants of **14** match those of **16a**-**16d**; therefore, these data may tentatively confirm the relative configuration of the three contiguous stereogenic centers. However, it must be pointed out that the intramolecular hydrogen bonds in **14** and **16a**-**16d** are different, which leads to uncertainty regarding the values of the coupling constants. Furthermore, because of the absence of the substituent at the 6 position, **16a**-**16d** may adopt different conformations compared with **14**. In 1988,

Figure 2.4 Reported coupling constants in bicyclic systems.[30a,b]



based on coupling constants,[30b] Ferris and Devades reported a conformational analysis in the pyrroloimidazole ring system **17a** and **17b**, which bears structural similarity with our bicyclic triazole **15a**, **15b**, and **15c** (Figure 2.5).[30c] Since **17a** and **17b** were fully protected, the impact of intramolecular hydrogen bonds is avoided. Their investigation revealed that the value of the *trans* coupling constant ($J_{5,6}$ in **17**) was 1.8 Hz, whereas the *cis* coupling constants ($J_{6,7}$ in **16** and **17**, $J_{5,6}$ in **16**) were 6.0 and 7.2 Hz, respectively.[30b]

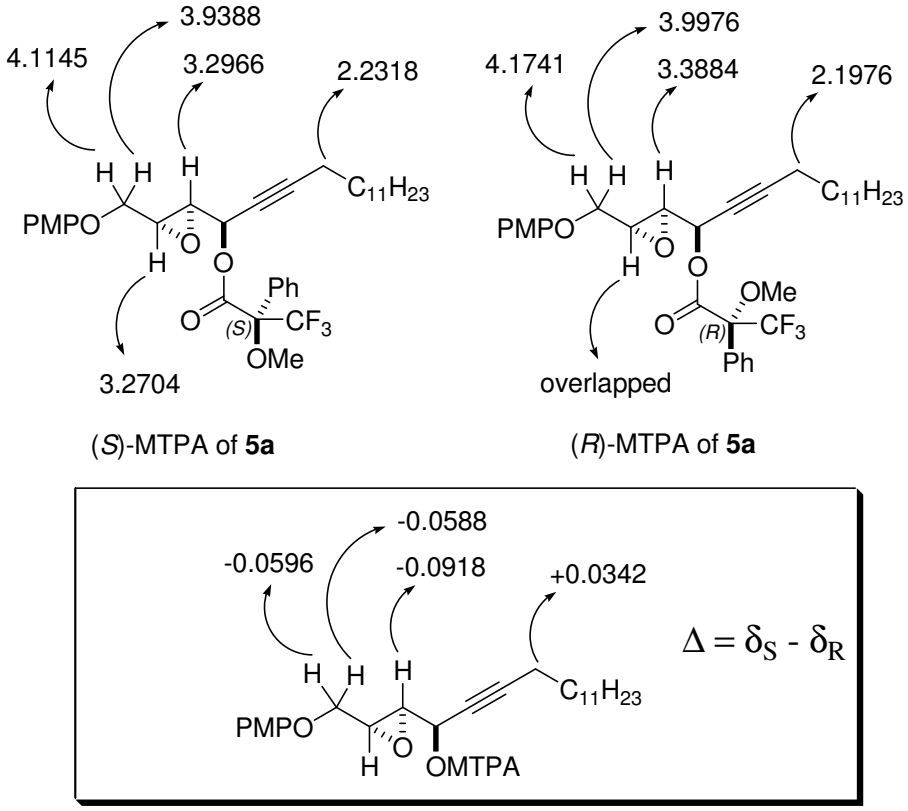
Figure 2.5 Partial ^{1}H-NMR spectra of **15a** (top) and **15b/15c** (ratio 1.2:1, bottom).



The coupling constants of *cis* $J_{4,5}$ and *trans* $J_{5,6}$ in bicyclic triazole **15a** (Figure 2.5) were expected to differ largely. However, to our surprise, we found that they have two very close *J* values ($J_{4,5}$ = 5.8 Hz and $J_{5,6}$ = 4.4 Hz). Furthermore, the two $J_{5,6}$ values of the *trans* coupling constants in **15a** and **15b** are markedly different (4.4 Hz in **15a**, 1.5 Hz in **15b**). Based on this analysis, it is possible that one of the known stereocontrolled steps did not proceed in the normal way. Therefore, we decided to verify the course of the construction of the three contiguous stereogenic centers by examining: (1) the configuration at C-4 in **5a** to check which enynol reacted [(*S*)-**6** or (*R*)-**6**] in SAE, (2) the configurations at the C-2 and C-3 positions in **5a**, and (3) the opening of **5a** to verify the configuration at C-2 of **3**.

Verification of the Sharpless Kinetic Resolution. According to the empirical rule established by Sharpless and co-workers, the Sharpless kinetic resolution of secondary alkyl allylic alcohols favors the reaction in which the *R* enantiomer of the racemic mixture forms the epoxide, while the *S* enantiomer is recovered in an optically enriched form when D-(-)-DIPT is used.[31] For allylic propargylic alcohols, the *S* enantiomer should react faster with D-(-)DIPT because the acetylenic moiety has a higher configurational priority than the olefinic group. Allylic propargylic alcohols have already been proved to uphold the empirical rule,[32] although the acetylenic moiety would cause less steric crowding in the transition states for SAE in comparison with alkyl groups. However, the verification is limited to hydrocarbon substrates.[32] In order to confirm the Sharpless kinetic resolution in our case, the (*R*)- and (*S*)-MTPA esters of **5a** were prepared to verify the configuration at C-4. Analysis of the $\Delta\delta$ values of the protons indicates that the reacted allylic propargylic alcohol was in fact (*S*)-**6**, confirming the prediction made by the empirical rule (Figure 2.6).

Figure 2.6 MTPA ester chemical shifts for determination of absolute configuration of **5a**



Epoxide Configuration in 5a. The absolute stereochemistry of an epoxide in chiral epoxy alcohols is generally assigned by the advanced Mosher method using (*R*)- and (*S*)-MTPA esters of the corresponding ring-opened diol or by established empirical mnemonics developed for different asymmetric epoxidation strategies.[33] Parker and Katsoulis[32c] determined the absolute configuration of the epoxide in propargylic epoxy alcohols by converting the epoxide to a 1,3-diol and analyzing the corresponding acetonide by the commonly used [^{13}C]-acetonide method developed by Rychnovsky et al.[34] This method needs a two-step derivatization. We selected the Et_2AlCl-catalyzed cyclization of epoxytrichloroacetimidates[35a] to transfer the

chiral information of the epoxide to the newly formed secondary hydroxy group in an oxazoline or dihydrooxazine (Scheme 2.5). Generally, cyclization takes place preferentially at the more polarized center of the epoxide with complete *inversion* of stereochemistry.[35a] As a result, after this transformation, the newly formed hydroxy group and C-4 oxygen in **13** will retain the same relative configuration as that in the epoxy alcohol between the epoxide and C-4 hydroxy group in **5a**. By determining the configuration of the newly formed hydroxy group, we can assign the configuration of the epoxide in **5a**.[35b] Reaction of **5a** with trichloroacetonitrile in the presence of Et_2AlCl and DBU gave the corresponding 2,3-epoxy-1-trichloroacetimidate, which delivered oxazoline **13** in a two-step yield of 76% (Scheme 2.5). The regiochemistry of cyclization was judged by analysis of the ^{1}H-^{1}H COSY spectrum of **13**. Analysis of the (*R*)- and (*S*)-MTPA esters of **13** ((*R*)-and (*S*)-**18**) revealed the *anti* relationship between the C-2 hydroxy group and C-4 oxygen (Figure 2.7), indicating that SAE of enynol (*S*)-**6** followed the normal prediction made by Sharpless et al. for allylic alcohols bearing saturated alkyl groups.

Scheme 2.5 Conversion of **5a** to (*S*)- and (*R*)-**18**

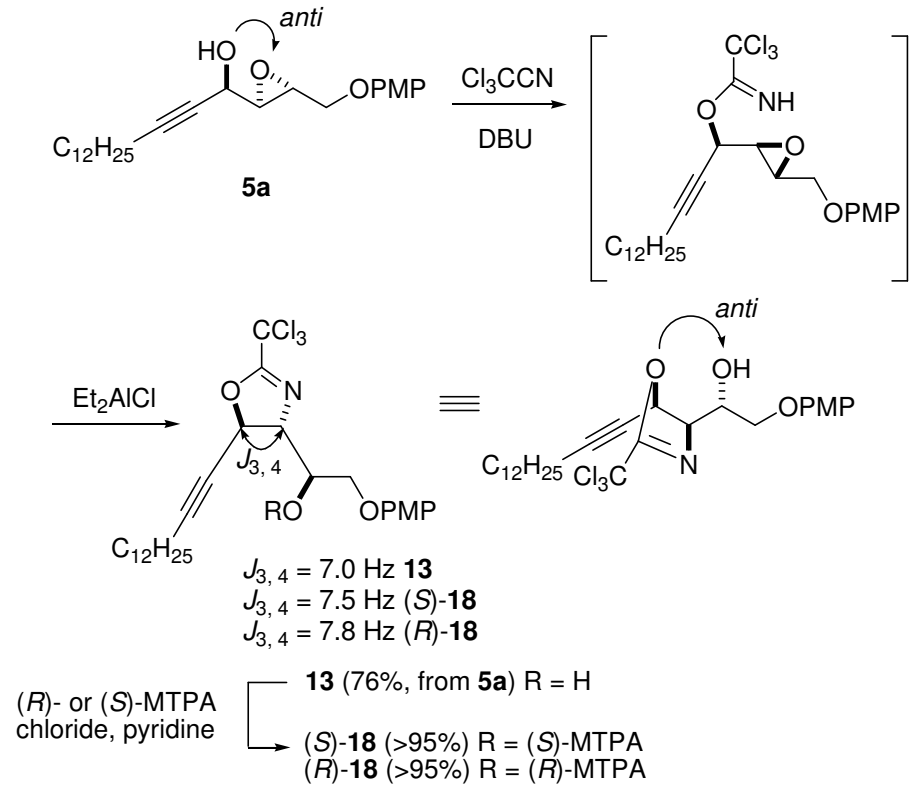
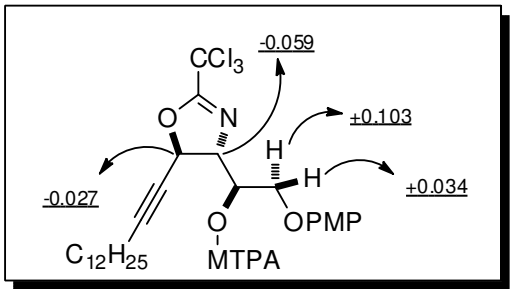


Figure 2.7 Absolute stereochemistry determination of **13** via the advanced Mosher method



Caption to Fig. 2: $\Delta\delta$ values for the MTPA derivatives (*S*)-**18** and (*R*)-**18** ($\Delta\delta = \delta_S - \delta_R$ ppm, 500 MHz).

Configuration of C-2. At this stage, the stereochemistry of the opening of epoxy alcohol **5a** (the first step of Scheme 2.4) requires verification. For this purpose, we planned to determine the configuration at C-2 of **3** by preparing the (*R*)- and (*S*)-MTPA amides (Scheme 2.6). Reaction of diol **3** with BnBr and NaH in the presence of a catalytic amount of TBAI provided azide **19** in 63% yield. Several methods were explored for the reduction of azide **19**. We found that azide **19** was smoothly converted to the corresponding amine **20** by using 1,3-propanedithiol as the reducing agent.[36] In situ reaction of **20** with (*R*)- and (*S*)-MTPA chlorides gave the (*S*)- and (*R*)-MTPA amides ((*S*)- and (*R*)-**21**), respectively. Analysis of the two MTPA amides demonstrated the *syn* relationship between the azide at C-2 and oxygen at C-4, indicating that opening of epoxy alcohol **5a** took place by a simple S_N2 conversion (Figure 2.8). Therefore, the evidence showed that the construction of the three contiguous stereogenic centers was correct. The almost identical *cis* and *trans* coupling constants in **15a** (*cis* $J_{4,5}$ and *trans* $J_{5,6}$) and the different *cis* coupling constants in **15a** ($J_{5,6}$) and **15b** ($J_{5,6}$) may result from the two different conformations they adopted. This result indicates the need for caution when coupling constants are used to judge the relative configuration in bicyclic triazoles and structurally similar systems.

Scheme 2.6 Conversion of Azido Diol **3** to (*S*)- and (*R*)-MTPA Amide **21**

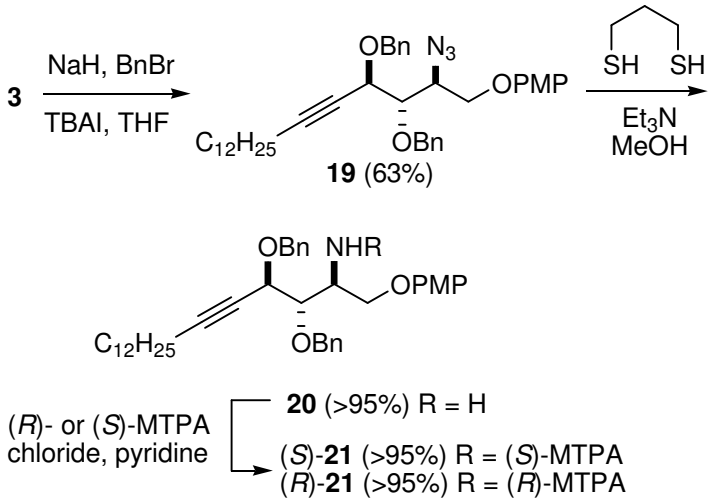
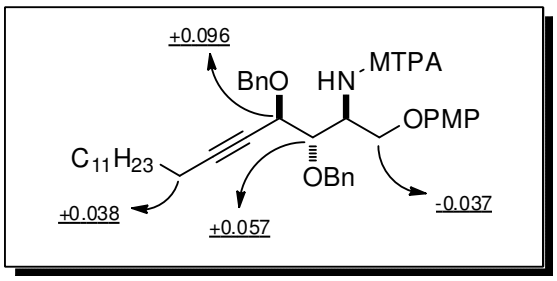


Figure 2.8 Absolute stereochemistry determination of **20** by the advanced Mosher method.



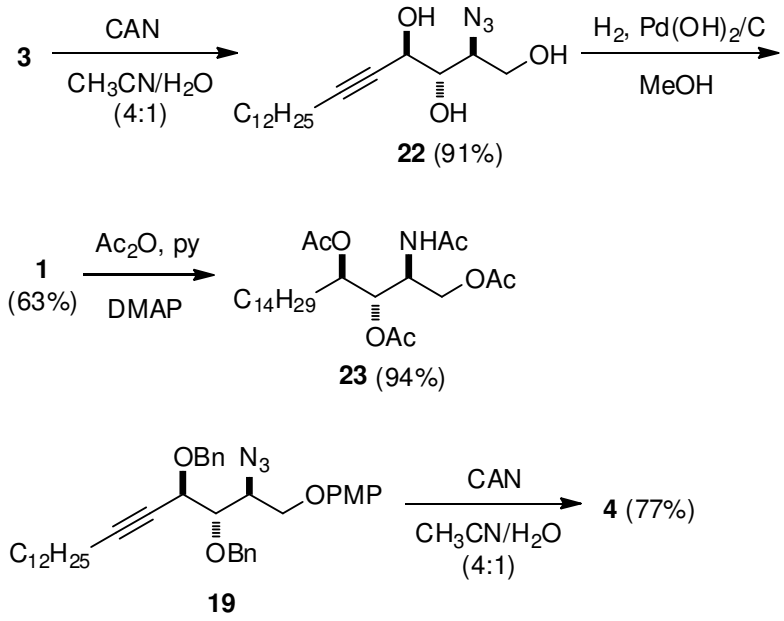
Caption to Fig. 2: $\Delta\delta$ values for the MTPA amides (*S*)-**21** and (*R*)-**21** ($\Delta\delta = \delta_S - \delta_R$ ppm, 500 MHz).

Completion of the Preparation of 1 and 4. As shown in Scheme 2.7, deprotection of the PMP group by CAN in **3** followed by hydrogenation of the resulting triol **22** using Pearlman's catalyst ($Pd(OH)_2/C$) in MeOH afforded **1**. Its ^1H and ^{13}C NMR spectra as well as specific rotation matched the previously reported

data.[9, 39] The structure of **1** was further confirmed by conversion to its tetraacetyl derivative **23**.

In the synthesis of glycosylceramides, the choice of the glycosyl acceptor is a critical consideration (together with the selection of the glycosyl donor). A free amino group at the C-2 position of the sphingolipid is not a viable choice in the acceptor; moreover, the amide functionality of ceramide is not suitable because it deactivates the primary hydroxy group of the acceptor through unfavorable hydrogen bonding interactions.[15] Since an azide is apparently devoid of hydrogen-bonding interactions with the adjacent hydroxy group and can be readily converted to an amide in two steps after the glycosidation reaction,[16] we decided to prepare **4**. The saturated analog of azido PHS **4** has been prepared from **1** by a tedious protecting group manipulation involving the conversion of an amino group to an azide.[37] In contrast, the preparation of 2-azido carbinol **4** (via deprotection of **19**) is an efficient route to a glycosyl acceptor based on the phytosphingosine backbone because the azide is introduced at an early stage of the synthesis. Since modification of the lipid chain length in α-galactosylceramide analogs influences an array of cytokines release from activated iNKT cells and demonstrates a profound relationship between structure and activity,[38] the synthetic route described here allows modification of the chain length with ease.

Scheme 2.7 Completion of the Syntheses of **1** and **4** from **3** and **19**, Respectively



2.4 Conclusion

A stereocontrolled synthetic route to **1** from aldehyde **9** and 1-tetradecyne (**7**) has been developed. HWE reaction of aldehyde **9**[19] and AlH_3 reduction provided allylic alcohol **11**, and PCC oxidation afforded α,β-unsaturated aldehyde **8**. Catalytic alkynylation of **8** with **7** and SAE of (*S*)-**6** followed by regioselective NaN_3/NH_4Cl opening of the resulting propargylic epoxy alcohol **5a** delivered (2*S*,3*S*,4*R*) azido diol **3** with the desired three contiguous stereogenic centers in good yield and high *ee* and *de*. Deprotection of **3** with CAN and catalytic hydrogenation gave **1**. A key intermediate, alkynyl-azido **3**, can be readily converted to an efficient glycosyl acceptor (**4**) via *O*,*O*-dibenzylation and CAN deprotection. The relative stereochemistry of final product **1** was assigned by NMR analysis of corresponding

MTPA esters and amides, and confirmed by comparison of NMR spectra and specific rotations of **1** and its tetraacetate derivative **23**. Stereochemical assignment by comparing *J* values with reported data in bicyclic triazoles **15a** and **15b**, generated by a copper-free intramolecular click reaction of **3**, was inconclusive.

2.5 Experimental Section

(*E*)-4-(4'-Methoxyphenoxy)-2-butenal (8). To a cooled, rapidly stirred suspension of PCC (15.0 g, 69.6 mmol) and Celite (16 g) in 250 mL of CH_2Cl_2 was added alcohol **11** (8.44 g, 43.5 mmol) in one portion. After the mixture had stirred for 3 h at rt, the resulting dark mixture was diluted with 150 mL of Et_2O. Filtration through a pad of Florisil left a dark solid residue that was washed with Et_2O. The filtrate was concentrated, and the residue was purified by flash chromatography (a gradient of hexane/EtOAc 6:1 to 3:1) to afford **8** (5.5 g, 66%) as a slightly yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 4.76 (dd, *J* = 1.9, 4.0 Hz, 2H), 6.46 (ddt, *J* = 15.8, 7.8, 1.9 Hz, 1H), 6.82-6.87 (m, 4H), 6.94 (dt, *J* = 15.8, 4.0 Hz, 1H), 9.62 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 67.1, 114.7, 115.6, 132.2, 151.3, 151.9, 154.3, 193.0.

(4S,2*E*)-1-(4'-Methoxyphenoxy)-2-octadecen-5-yn-4-ol ((*S*)-6). A flame-dried round-bottom flask was charged with commercially available Trost's ProPhenol ligand (*R*,*R*)-**12** (1.0 g, 1.57 mmol), alkyne **7** (9.2 g, 47.1 mmol), and 300 mL of toluene. A solution of Me_2Zn (39.3 mL, 1.2 M in toluene, 47.1 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 **8** (3.0 g, 15.6 mmol) in a

minimal amount of toluene was added via syringe over *ca*. 10 s. The reaction mixture was sealed and cooled to 4 °C for 4 days without stirring. Then the reaction mixture 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 phase was dried (Na_2SO_4), filtered, and concentrated. Purification of the residue by flash chromatography (a gradient of hexane/EtOAc 6:1 to 7:2) provided (*S*)-**6** (5.2 g, 86%, 60% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.19-1.40 (m, 18H), 1.46-1.54 (m, 2H), 2.21 (dt, *J* = 2.0, 7.2 Hz, 2H), 2.45 (d, *J* = 4.3 Hz, 1H), 3.74 (s, 3H), 4.46-4.49 (m, 2H), 4.88-4.92 (m, 1H), 5.95 (ddt, *J* = 5.3, 15.4, 1.4 Hz, 1H), 6.08 (ddt, *J* = 1.2, 15.4, 5.3 Hz, 1H), 6.78-6.85 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 18.6, 22.6, 28.5, 28.8, 29.0, 29.3, 29.4, 29.5, 29.6, 31.8, 55.5, 62.3, 68.0, 78.8, 87.2, 114.5, 115.5, 127.1, 132.4, 152.5, 153.7; ESI-HRMS $[M+Na]^+$ calcd for *m*/*z* $C_{25}H_{38}NaO_3^+$ 409.2713, found 409.2717.

(4*R*,2*E*)-1-(4'-Methoxyphenoxy)-2-octadecen-5-yn-4-ol ((*R*)-6). (*R*)-**6** was prepared in 82% yield and 85% ee according to the procedure used to prepare (*S*)-**6**. The ^{1}H and ^{13}C NMR spectra were identical to those of (*S*)-**6**; ESI-HRMS $[M+Na]^+$ calcd for *m*/*z* $C_{25}H_{38}NaO_3^+$ 409.2713, found 409.2715.

General Preparation and Analysis of MTPA Esters or Amide. The reactions were generally run on a 0.02-mmol scale. A mixture of pyridine (4.0 equiv) and substrate (1.0 equiv) in CH_2Cl_2 (0.6 mL) was treated with neat (*R*)- or (*S*)-MTPA chloride (3.0 equiv). The solution was stored in a desiccator until no starting material was observed by TLC. It is important to monitor the reaction by TLC to ensure complete reaction, because kinetic resolution of an incomplete

reaction may significantly alter the ee or de measurements. The reaction mixture was passed through a short plug of silica gel to remove polar impurities, and the plug was washed with EtOAc/hexane (the ratio made the $R_f = 0.5$). After the filtrate was concentrated, the residue was dried under high vacuum (0.2 Torr, 1 h) and dissolved in $CDCl_3$. The (*S*)- and (*R*)-MTPA esters and amides were prepared by using (*R*)- and (*S*)-MTPA chlorides, respectively.

(*R*)-1-{(2'*R*,3'*R*)-3'-[(4''-Methoxyphenoxy)methyl]oxiran-2'-yl}pentadec-2-yn-1-ol (5a). 4Å Molecular sieves (the amount is not critical if the allyl propargyl alcohol, CH_2Cl_2, and cumene hydroperoxide are pre-dried) were added to a solution of D-(-)-DIPT (363 mg, 1.55 mmol) in 50 mL of dry CH_2Cl_2. The mixture was stirred at rt for 30 min before it was cooled to -40 °C. Ti(O-*i*-Pr)$_4$ (367 mg, 1.29 mmol) was added to the reaction mixture, which was stirred for 30 min. After cumene hydroperoxide (590 mg, 80% technical grade, 3.10 mmol) was added, the reaction mixture was stirred for 30 min. A solution of (*S*)-**6** (1.33 g, 3.45 mmol, 60% ee) in a minimal amount of dry CH_2Cl_2 was added, and the reaction mixture was sealed and stored at -20 °C without stirring for 3 days. An aqueous pre-cooled (0 °C) solution of tartaric acid (10 mL, 10% w/v) was added dropwise, and the mixture was allowed to warm to rt over 1 h, after which time the solution became transparent. The organic layer was separated, washed with brine, and concentrated. The residue was dissolved in Et_2O at 0 °C, and the solution was treated with a solution (4 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 Na_2SO_4. The

solvent was evaporated, and the residue was purified by flash chromatography (hexane/EtOAc 5:1 to 4:1) to afford **5a** (949 mg, 68% (maximum yield, 75%), 93% de); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.20-1.41 (m, 18H), 1.47-1.55 (m, 2H), 2.03 (br s, 1H), 2.22 (dt, *J* = 7.2, 1.9 Hz, 2H), 3.30 (t, *J* = 2.5 Hz, 1H), 3.50-3.53 (m, 1H), 3.77 (s, 3H), 3.99 (dd, *J* = 11.5, 5.3 Hz, 1H), 4.26 (dd, *J* = 11.5, 2.7 Hz, 1H), 4.65-4.68 (m, 1H), 6.80-6.88 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 18.7, 22.7, 28.4, 28.9, 29.1, 29.3, 29.5, 29.63, 29.65, 31.9, 53.8, 55.7, 57.4, 60.8, 68.0, 76.0, 88.1, 114.6, 115.8, 152.5, 154.2; ESI-HRMS [M+NH_4^+] calcd for *m*/*z* $C_{25}H_{42}NO_4^+$ 420.3108, found 420.3114.

(*S*)-1-{(2'*R*,3'*R*)-3'-[(4''-Methoxyphenoxy)methyl]oxiran-2'-yl}pentadec-2-yn-1-ol (5b). Compound **5b** was obtained together with **5c** and **5a** in a ratio of (**5b/5c/5a** 61:29:10) from (*R*)-**6** according to the procedure used to prepare **5a**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.22-1.40 (m, 18H), 1.47-1.55 (m, 2H), 2.22 (dt, *J* = 7.2, 1.9 Hz, 2H), 3.27 (dd, *J* = 2.2, 4.1 Hz, 1H), 3.40-3.43 (m, 1H), 3.77 (s, 3H), 3.98 (dd, *J* = 11.5, 5.3 Hz, 1H), 4.23 (dd, *J* = 11.5, 2.9 Hz, 1H), 4.38-4.42 (m, 1H), 6.81-6.88 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 18.7, 22.7, 28.4, 28.9, 29.1, 29.3, 29.5, 29.62, 29.64, 31.9, 54.2, 55.7, 58.2, 60.4, 61.8, 76.9, 87.6, 114.6, 115.7, 152.5, 154.2.

(1*S*)-2-(4'-Methoxyphenoxy)-1-[(4'*R*,5'*R*)-2'-(trichloromethyl)-4',5'-dihydro-5'-(tetradec-1''-ynyl)oxazol-4'-yl]ethanol (13). To an ice-cold solution of **5a** (30 mg, 74.5 μmol) in 1 mL of CH_2Cl_2 were added DBU (1.1 μL, 7.5 μmol) and trichloroacetonitrile (15 μL, 149 μmol). After being stirred at 0 °C until no starting material was observed on TLC, the reaction mixture was diluted with CH_2Cl_2 (10

mL), quenched with saturated NH_4Cl solution (5 mL), and extracted with CH_2Cl_2. The combined organic extracts were washed with saturated aqueous NH_4Cl solution, dried (Na_2SO_4), and concentrated. The residue was dissolved in Et_2O and passed through a short column packed with anhydrous Na_2SO_4 and silica gel. Evaporation of Et_2O gave a residue that was dried under high vacuum (0.2 Torr, overnight) and used directly in the subsequent cyclization reaction without further purification.

To an ice-cold solution of epoxy trichloroacetimidates in CH_2Cl_2 (1 mL) was added Et_2AlCl (37.3 μL, 1.0 M solution in hexane, 37.3 μmol). After being stirred at rt until no starting material was observed on TLC, the reaction mixture was quenched with saturated $NaHCO_3$ solution. The reaction mixture was diluted with Et_2O, washed with water, dried, and evaporated. The residue was purified by flash chromatography (hexane/EtOAc 5:1) to afford oxazoline **13** (31 mg, 76%); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.21-1.36 (m, 18H), 1.43-1.50 (m, 2H), 2.21 (dt, *J* = 1.9, 7.1 Hz, 2H), 2.48 (d, *J* = 4.8 Hz, 1H), 3.77 (s, 3H), 4.05 (dd, *J* = 6.0, 9.5 Hz, 1H), 4.12 (dd, *J* = 4.2, 9.5 Hz, 1H), 4.15-4.20 (m, 1H), 4.46 (dd, *J* = 5.8, 7.0 Hz, 1H), 5.61 (dt, *J* = 1.9, 7.0 Hz, 1H), 6.81-6.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.8, 22.7, 28.2, 28.8, 29.1, 29.3, 29.5, 29.62, 29.63, 29.66, 31.9, 55.7, 69.5, 70.5, 74.9, 75.8, 76.1, 91.2, 114.7, 115.6, 152.3, 154.3, 162.7; ESI-HRMS $[M+H]^+$ calcd for *m*/*z* $C_{27}H_{38}Cl_3NO_4^+$ 546.1939, found 546.1944.

(2*S*,3*S*,4*R*)-1-(4'-Methoxyphenoxy)-2-azidooctadec-5-yne-3,4-diol (3). To epoxy alcohol **5a** (95 mg, 0.246 mmol) in 4.5 mL of MeOH/H_2O (8:1) were added NH_4Cl (66 mg, 1.23 mmol) and NaN_3 (160 mg, 2.46 mmol). 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 × 10 mL). The combined extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (elution with EtOAc/hexane, 5:1 to 3:1 to 5:2) afforded **3** (68 mg, 62%); $[\alpha]^{25}_D$ +22.8 (*c* 1.2, MeOH); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.19-1.33 (m, 16H), 1.33-1.41 (m, 2H), 1.48-1.56 (m, 2H), 2.25 (dt, *J* = 2.0, 7.1 Hz, 2H), 2.53 (br s, 1H), 2.60 (br s, 1H), 3.76-3.80 (m, 4H), 3.85-3.90 (m, 1H), 4.18 (dd, *J* = 7.1, 10.0 Hz, 1H), 4.42 (dd, *J* = 3.3, 10.0 Hz, 1H), 4.67-4.71 (m, 1H), 6.82-6.91 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.1, 18.7, 22.7, 28.5, 28.9, 29.1, 29.3, 29.5, 29.6, 29.7, 31.9, 55.7, 62.2, 64.4, 69.1, 72.7, 76.1, 89.3, 114.7, 115.7, 152.3, 154.3; ESI-HRMS $[M+Na]^+$ calcd for *m/z* $C_{25}H_{39}N_3NaO_4^+$ 468.2833, found 468.2834.

(4*R*,5*S*,6*S*)-6-[(4'-Methoxyphenoxy)methyl]-3-dodecyl-5,6-dihydro-4*H*-pyrrolo[1,2-c][1,2,3]triazole-4,5-diol (14). A solution of 20 mg (45 μmol) of diol **3** in 2 mL of toluene was stirred at 90 °C for 48 h. The solvent was evaporated and the residue was purified by column chromatography (elution with hexane/EtOAc 1:1 to 2:3) to provide **14** (19 mg, 95%); $[\alpha]^{25}_D$ -20.8 (*c* 0.48, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.19-1.39 (m, 16H), 1.53-1.65 (m, 4H), 1.66-1.75 (m, 2H), 2.71 (t, *J* = 7.7 Hz, 2H), 3.75 (s, 3H), 4.42-4.46 (m, 1H), 4.48-4.53 (m, 1H), 4.73 (q, *J* = 3.4 Hz, 1H), 4.96-4.99 (m, 1H), 5.21 (d, *J* = 5.5 Hz, 1H), 6.72-6.80 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.4, 29.1, 29.4, 29.62, 29.65, 29.68, 31.9, 55.7, 64.5, 64.8, 66.9, 77.9, 114.7, 115.9, 137.8, 143.3, 152.0, 154.6; ESI-HRMS $[M+H]^+$ calcd for *m/z* $C_{25}H_{40}N_3O_4^+$ 446.3013, found 446.3006.

(4*R*,5*S*,6*S*)-6-[(4'-Methoxyphenoxy)methyl]-3-dodecyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-4,5-di-yl Acetate (15a). To a solution of 10 mg (22 μmol) of **14** in 1 mL of CH_2Cl_2 was added 100 μL (717 μmol) of Et_3N and 50 μL (530 μmol) 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 amount of CH_2Cl_2, and filtered through a pad of silica gel in a buret. The pad was rinsed with 10 mL of hexane/EtOAc 4:1. Concentration gave diacetate **15** (11 mg, 98%) as a colorless syrup. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.20-1.37 (m, 18H), 1.61-1.70 (m, 2H), 2.13 (s, 3H), 2.14 (s, 3H), 2.73 (t, *J* = 7.7 Hz, 2H), 3.75 (s, 3H), 4.48 (dd, *J* = 2.7, 10.4 Hz, 1H), 4.59 (dd, *J* = 3.0, 10.4 Hz, 1H), 4.87 (dt, *J* = 4.3, 2.9 Hz, 1H), 6.05 (dd, *J* = 4.3, 5.7 Hz, 1H), 6.31 (d, *J* = 5.8 Hz, 1H), 6.73-6.81 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 20.4, 20.5, 22.7, 25.3, 29.2, 29.3, 29.4, 29.57, 29.62, 29.64, 29.7, 31.9, 55.6, 62.2, 64.6, 66.4, 76.8, 114.6, 116.1, 134.6, 143.7, 151.7, 154.7, 169.5, 169.6.

(4*S*,5*S*,6*S*)-6-[(4'-Methoxyphenoxy)methyl]-3-dodecyl-5,6-dihydro-4H-pyrrolo[1,2-c][1,2,3]triazol-4,5-di-yl Acetate (15b). Compound **15b** was prepared along with **15c** from the mixture of **5b**, **5c**, and **5a** (61:29:10) according to the same sequence used to convert **5a** to **15a** (ratio of **15b**: **15c** = 1.2:1). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.2 Hz, 3H), 1.20-1.37 (m, 18H), 1.61-1.70 (m, 2H), 2.14 (s, 3H), 2.15 (s, 3H), 2.69-2.72 (m, 2H), 3.76 (s, 3H), 4.51-4.53 (m, 2H), 4.72-4.75 (m, 1H), 5.85 (dd, *J* = 1.5, 1.9 Hz, 1H), 6.03 (d, *J* = 1.3 Hz, 1H), 6.73-6.81 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.4, 20.5, 22.7, 25.3, 29.2, 29.3, 29.4, 29.57,

29.62, 29.64, 29.7, 31.8, 55.6, 64.0, 67.0, 69.4, 84.3, 114.6, 115.8, 134.9, 143.6, 151.9, 154.5, 169.7, 169.8.

(2*S*,3*S*,4*R*)-1-(4'-Methoxyphenyl)-2-azido-3,4-benzyloxy-5-octadecyn-1,3,4-triol (19). To a mixture of 222 mg (5.56 mmol) of NaH (60%) and 620 mg (1.39 mol) of diol **3** in 10 mL of freshly distilled THF were added 343 μL (6.95 mmol) of benzyl bromide and 3 mg (8 μmol) of TBAI at rt. The mixture was stirred at rt overnight and then was quenched with 5 mL of MeOH. The reaction mixture was poured into a mixture of ice and EtOAc. The organic layer was separated, washed with aqueous 1 M HCl, water, saturated aqueous $NaHCO_3$ solution, and brine, and then dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by flash chromatography (hexane/EtOAc 40:1) to afford **19** (546 mg, 63%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3H), 1.20-1.30 (m, 12H), 1.37-1.44 (m, 2H), 1.51-1.60 (m, 2H), 2.28 (dt, J = 1.6, 7.0 Hz, 2H), 3.77 (s, 3H), 3.82 (t, J = 4.9 Hz, 1H), 4.00-4.06 (m, 2H), 4.18-4.23 (m, 1H), 4.40-4.42 (m, 1H), 4.51 (d, J = 11.6 Hz, 1H), 4.65 (d, J = 11.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.9, 22.7, 28.6, 29.0, 29.2, 29.4, 29.55, 29.64, 29.66, 31.9, 55.7, 61.5, 68.3, 70.0, 70.8, 74.3, 75.6, 80.1, 89.1, 114.6, 115.6, 127.8, 128.0, 128.2, 128.3, 128.4, 137.6, 137.8, 152.5, 154.1; ESI-HRMS $[M+Na]^+$ calcd for m/z $C_{39}H_{51}N_3O_4Na^+$ 648.3772, found 648.3776.

(2*S*,3*S*,4*R*)-1-(4'-Methoxyphenoxy)-3,4-bis(benzyloxy)octadec-5-yn-2-amine (20). To a solution of **19** (23 mg, 37 μmol) in MeOH (1 mL) were added Et_3N (102 μL, 0.73 mmol) and 1,3-dithiopropane (73 μL, 0.73 mmol). The reaction mixture was stirred overnight at 50 °C. The white precipitate was removed by

filtration and washed twice with MeOH. After the solvent was evaporated, the residue was dried under high vacuum (0.2 Torr, overnight) and used directly in the subsequent MTPA ester analysis without further purification.

(2*S*,3*S*,4*R*)-2-Azidooctadec-5-yne-1,3,4-triol (22). Diol **3** (75 mg, 0.17 mmol) was dissolved in 2.5 mL of CH_3CN/H_2O (4:1) at rt, and CAN (461 mg, 0.84 mmol) was added. The mixture was stirred at rt until completion as monitored by TLC (about 1 h) and diluted with $CHCl_3$. The resulting solution was washed with H_2O and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (hexane/EtOAc 3:2) to afford triol **22** (52 mg, 91%); $[\alpha]^{25}_D$ +43.2 (*c* 0.5, MeOH); ^{1}H NMR (500 MHz, CD_3OD) δ 0.90 (t, *J* = 7.1 Hz, 3H), 1.23-1.35 (m, 16H), 1.39-1.46 (m, 2H), 1.49-1.56 (m, 2H), 2.25 (dt, *J* = 2.0, 7.0 Hz, 2H), 3.52-3.57 (m, 2H), 3.69 (dd, *J* = 7.2, 11.5 Hz, 1H), 3.96-4.00 (m, 1H), 4.45-4.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.7, 22.7, 28.5, 28.9, 29.1, 29.3, 29.5, 29.62, 29.65, 31.9, 62.7, 63.9, 64.2, 73.7, 76.2, 89.3; ESI-HRMS $[M+Na]^+$ calcd for *m*/*z* $C_{18}H_{33}N_3O_3Na^+$ 362.2414, found 362.2412.

D-*ribo*-Phytosphingosine (1). To a solution of 34 mg (0.10 mmol) of triol **22** in 5 mL of MeOH was added 11 mg (0.020 mmol) of 20% $Pd(OH)_2/C$. The resulting suspension was degassed three times and was stirred with a balloon filled with H_2 overnight. The crude reaction mixture was filtered through a short pad of Celite, which was washed with 30 mL of MeOH. The combined filtrates were concentrated and purified by flash chromatography ($CHCl_3$/MeOH/concd NH_4OH 130:25:4) to afford **1** (20 mg, 63%) as a white solid. The product was dissolved in a minimum volume of $CHCl_3$ and passed through a 0.45-μm filter to remove the suspended

silica gel; mp 99-101 °C [lit.[9] mp 98.5-101.5 °C]; $[\alpha]^{25}_{D}$ +8.0 (*c* 0.8, C_5H_5N) [lit.[9] $[\alpha]^{25}_{D}$ +7.3 (*c* 0.9, C_5H_5N)]; ^{1}H NMR (500 MHz, CD_3OD) δ 0.89 (t, *J* = 7.1 Hz, 3H), 1.22-1.41 (m, 24H), 1.49-1.60 (m, 1H), 1.68-1.77 (m, 1H), 2.94-2.97 (m, 1H), 3.33 (dd, *J* = 5.4, 7.8 Hz, 1H), 3.47-3.52 (m, 1H), 3.55 (dd, *J* = 6.8, 10.9 Hz, 1H), 3.75 (dd, *J* = 4.1, 10.9 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 14.4, 23.8, 26.6, 30.5, 30.79, 30.82, 31.0, 33.1, 34.8, 55.8, 64.0, 74.4, 76.4; ESI-HRMS $[M+Na]^+$ calcd for *m/z* $C_{18}H_{39}NNaO_3^+$ 340.2822, found 340.2823.

D-*ribo*-Phytosphingosine Tetraacetate (23). Compound **23** was prepared from **1** according to ref. 9. $[\alpha]^{25}_{D}$ +22.6 (*c* 0.7, $CHCl_3$) [lit.[39] $[\alpha]^{20}_{D}$ +21.9 (*c* 1.1, $CHCl_3$)]; ^{1}H NMR (500 MHz, $CHCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.16-1.39 (m, 24H), 1.57-1.72 (m, 2H), 2.03 (s, 1H), 2.05 (s, 6H), 2.09 (s, 3H), 4.00 (dd, *J* = 2.8, 11.7 Hz, 1H), 4.29 (dd, *J* = 4.7, 11.7 Hz, 1H), 4.44-4.51 (m, 1H), 4.93 (t, *J* = 9.9, 2.8 Hz, 1H), 5.11 (dd, *J* = 2.8, 8.4 Hz, 1H), 6.06 (d, *J* = 9.4 Hz, 1H); ^{13}C NMR (125 MHz, $CHCl_3$) δ 14.1, 20.75, 20.78, 21.1, 22.7, 23.3, 25.5, 28.0, 29.28, 29.34, 29.5, 29.57, 29.61, 29.64, 29.66, 31.9, 47.5, 62.8, 71.8, 73.0, 169.8, 170.1, 170.9, 171.2.

(2*S*,3*S*,4*R*)-2-Azido-3,4-bis(benzyloxy)octadec-5-yn-1-ol (4). Compound **19** (546 mg, 0.872 mmol) was dissolved in 25 mL of CH_3CN/H_2O (4:1) at rt, and CAN (2.39 g, 4.36 mmol) was added. The mixture was stirred at rt until completed as monitored by TLC (about 1 h) and diluted with $CHCl_3$. The resulting solution was washed with H_2O and brine. The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (elution with hexane/EtOAc 10:1 to 6:1) to afford 349 mg (77%) of alcohol **4** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.20-1.33 (m, 16H), 1.36-

1.45 (m, 2H), 1.50-1.58 (m, 2H), 2.28 (dt, *J* = 1.9, 7.1 Hz, 2H), 2.32 (br s, 1H), 3.72-3.81 (m, 3H), 3.81-3.87 (m, 1H), 4.37-4.40 (m, 1H), 4.50 (d, *J* = 11.8 Hz, 1H), 4.63 (d, *J* = 11.4 Hz, 1H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.86 (d, *J* = 11.8 Hz, 1H), 7.26-7.38 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 18.8, 22.7, 28.6, 28.9, 29.1, 29.3, 29.5, 29.60, 29.63, 31.9, 62.1, 63.0, 69.6, 70.7, 73.9, 75.3, 80.8, 89.3, 127.85, 127.89, 128.0, 128.1, 128.38, 128.39, 137.3, 137.5; ESI-HRMS $[M+Na]^+$ calcd for *m/z* $C_{32}H_{45}N_3NaO_3^+$ 542.3353, found 542.3356.

2.6 References and Notes

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Sigma-Aldrich: $[\alpha]^{25}_{D}$ +50 (*c* 1.0, $CHCl_3$)]; (*R*,*R*)-**12**: $[\alpha]^{25}_{D}$ -40.9 (*c* 0.65, $CHCl_3$), [Sigma-Aldrich: $[\alpha]^{25}_{D}$ -50 (*c* 1.0, $CHCl_3$)].

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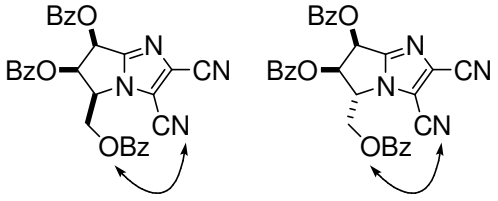

17a **17b**

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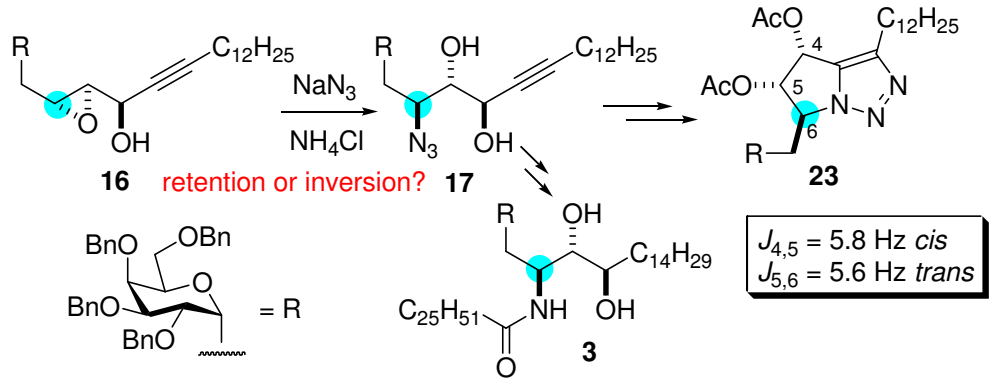
Chapter 3: Verification of Configurations of Three Contiguous Stereogenic Centers in the Phytosphingosine Backbone of α-1*C*-GalCer

3.1 Abstract



This Chapter describes: (1) an improved synthesis of α-1*C*-galactosylceramide **3** via the two-step HWE olefination and alane reduction protocol described in Chapter 1 and the ProPhenol-catalyzed asymmetric alkynylation reaction discussed in Chapter 2, and (2) verification of the stereochemical configurations of three contiguous stereogenic centers in the phytosphingosine moiety of **3**. Given the possible intramolecular participation by the 2'-*O*-benzyl group involved in the opening of epoxide **16** by azide anion, assignment of the relative stereochemistry of the azide-bearing carbon in **17** was initially attempted from analysis of the coupling constants ($J_{4,5}$ and $J_{5,6}$) of bicyclic triazole **23**, which was obtained via an intramolecular click reaction and *O*-acetylation of diol **17**. The *cis* $J_{4,5}$ and *trans* $J_{5,6}$ coupling constants displayed almost the same values, suggestive of possible

retention in the opening of epoxide **16**. The retention of the epoxide-opening of **16** based on nOe investigation of **23** was inconclusive. Model compounds **27a**, **27b**, and **31** containing the same bicyclic triazole skeleton were prepared via the same reaction sequence from epoxy alcohols **26** and **30**, respectively. The *cis* $J_{4,5}$ and *trans* $J_{5,6}$ coupling constants in **27a**, **27b**, and **31** showed similar values to those in **23**. On the basis of the systematical investigation of model compound **31** described in Chapter 2, it was concluded that the epoxide-opening reaction of **16** did indeed proceed with inversion, excluding intramolecular participation by the 2'-*O*-benzyl group. This study underscores the need for caution when coupling constants alone are used to judge the relative configuration in bicyclic triazoles and structurally similar systems.

3.2 Introduction

The synthetic glycosphingolipid KRN7000 [(2*S*,3*S*,4*R*)-1-*O*-(α-D-galactopyranosyl)-2-(*N*-hexacosanoylamino)-1,3,4-octadecanetriol, α-GalCer, **1**, Figure 3.1, P.60] was derived from a lipid in the marine sponge *Agelas mauritianus*. Compound **1** is the first exogenous antigen that could be presented by CD1d, a glycoprotein on the surface of antigen-presenting cells, to the receptor on the surface of iNKT cells.[1] Upon stimulation, iNKT cells rapidly secrete copious amounts of T helper 1 (Th1) and T helper 2 (Th2) cytokines IFN-γ and IL-4, respectively, to modulate the immune system.[2] Stimulation of iNKT cells is followed by secondary activation of other cells in the immune system, such as natural killer (NK) cells,

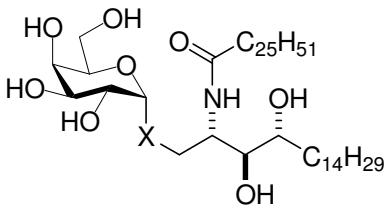
dendritic cells, macrophages, B cells, and conventional T cells.[3] Many of these cells secrete additional immune modulating cytokines, creating an entire activation cascade. Therefore, activation of iNKT cells by α-GalCer can influence both innate and adaptive immune responses and play a pivotal role in regulating immune responses in both host defense and autoimmume diseases.[4]

The production of Th1 cytokines is thought to correlate with antitumor, antiviral/antibacterial, and adjuvant activities, whereas Th2 cytokine production is thought to subdue autoimmune diseases. However, production of Th2 may mask the beneficial effects of Th1 and limit the therapeutic efficiency of α-GalCer.[5] Thus, extensive efforts have been made to develop analogs of **1** that can activate iNKT cells to selectively release either Th1- or Th2-type cytokines. Indeed, many studies found that modifications of the phytosphingosine backbone of **1** result in marked changes in immunomodulatory activity on iNKT cell activation. For example, introduction of an aryl substituent into the N-acyl chain provided analogs of **1** that elicited a bias toward a Th1-type cytokine response,[6] whereas truncation of either chain or installation of two nonconjugated *cis* double bonds into the N-(C20)-acyl chain stimulated Th2-biased cytokine production in iNKT cells in vitro.[7]

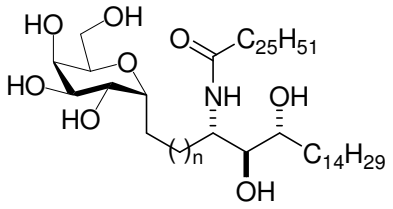
α-*C*-Glycosides are resistant to α-glycosidase activity, and therefore may have longer half-lives than α-*O*-glycosides on the surface of antigen-presenting cells. Moreover, replacing the glycosidic oxygen atom with a methylene group removes a hydrogen-bonding acceptor site.[8] Small modifications in the linker region between the sugar and lipid were found by Franck, Tsuji, and coworkers[9] and by our laboratory[10] to result in important activity differences. An isosteric *C*-glycoside

analog (**2**, Figure 3.1) was highly active in mice in vivo, with a biased induction of Th1 responses compared to **1**.[9a-d] In addition, in this in vivo study, **2** produced a longer term production of IFN-γ in mice, suggesting that the *C*-glycoside analog does not induce iNKT anergy. In 2006, the Bittman and Metelitsa laboratories reported that a nonisosteric α-1*C*-GalCer analog (**3**), in which the glycosidic oxygen was deleted so that the anomeric carbon was linked directly to C-1 of phytosphingosine, induced a higher Th1-type cytokine response than **1** and **2** in human iNKT cells in vitro.[10] Interestingly, other *C*-glycoside homologues that contain a 3-carbon linker (**4**) are inactive.[9b] The Franck and Tsuji laboratories reported that GCK127 (**5**), an analog with an *E*-alkene linker, not only exhibited activity in mice, but also induced a potent stimulatory activity against human iNKT cells, which was ascribed to the preservation of an ~170° dihedral angle in the linker region between the galactose and the ceramide (Gal-C1-O1-phytosphingosine C1'-phytosphingosine C2').[9e-g] However, the analog with an *Z*-alkene linker (**6**) showed no activity.[9e] An analog containing an acetylenic linker (**7** in Figure 3.1, compound **6** in Chapter 4, p. 86) demonstrated some activity, but much lower than that of **2**.[11]

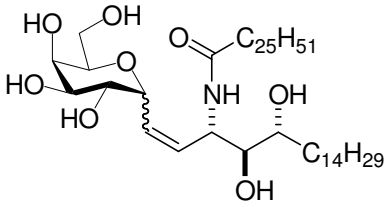
Figure 3.1 Structures of KRN7000 and analogs **2**-**7**



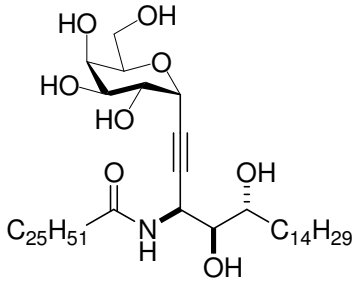
1 X = O KRN7000
2 X = CH_2 α-*C*-GalCer



3 n = 0 α-1*C*-GalCer
4 n = 2



5 *E*-alkene (GCK127)
6 *Z*-alkene

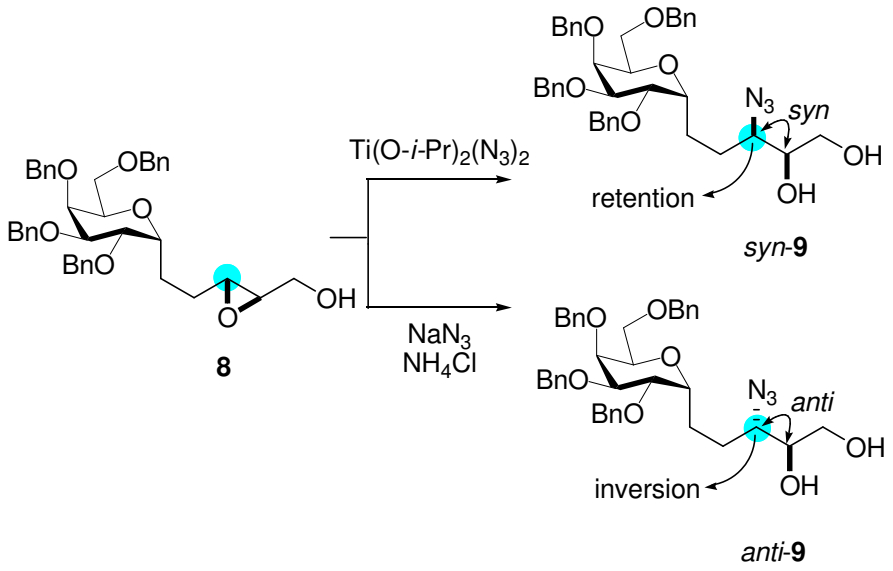


7 alkynyl-linked α-*C*-GalCer

Recently, Pu and Franck prepared α-*C*-GalCer diastereomers via Sharpless asymmetric epoxidation (SAE) chemistry.[9c] They found an unusual phenomenon during the opening of hydroxy epoxide **8**; opening with NaN_3/NH_4Cl provided an *anti* vicinal azido diol *anti*-**9** with inversion of configuration at the N_3-bearing carbon, whereas opening with $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ gave *syn* vicinal azido diol *syn*-**9** with retention (Scheme 3.1). The mechanism of retention is unclear, but the reason might be the intramolecular participation by the pyranosidic oxygen atom or the 2'-*O*-benzyl group to form an intermediate oxonium ion, thus inverting the epoxide center.[9c] The synthetic route to **3** reported in this Chapter also involves the use of SAE followed by the opening of epoxide to construct three contiguous stereogenic centers in the phytosphingosine moiety. In order to facilitate SAR research and

synthesis of other analogs derived from **3**, we sought to verify its stereochemical structure. In this Chapter, a method is reported to achieve this goal that is centered on the intramolecular click reaction.[12] This Chapter also describes the development of an improved route to **3**, which has allowed us to make a larger quantity of analog **3** available to the immunology community. The main improvement of this route includes the use of our recently developed two-step HWE olefination/AlH_3 reduction protocol (Chapter 1)[13] and the ProPhenol-catalyzed asymmetric alkynylation developed by Trost and coworkers (discussed in Chapter 2).[14]

Scheme 3.1 Retention and Inversion of Opening of Epoxide in the Synthesis of α-*C*-GalCer (**2**)

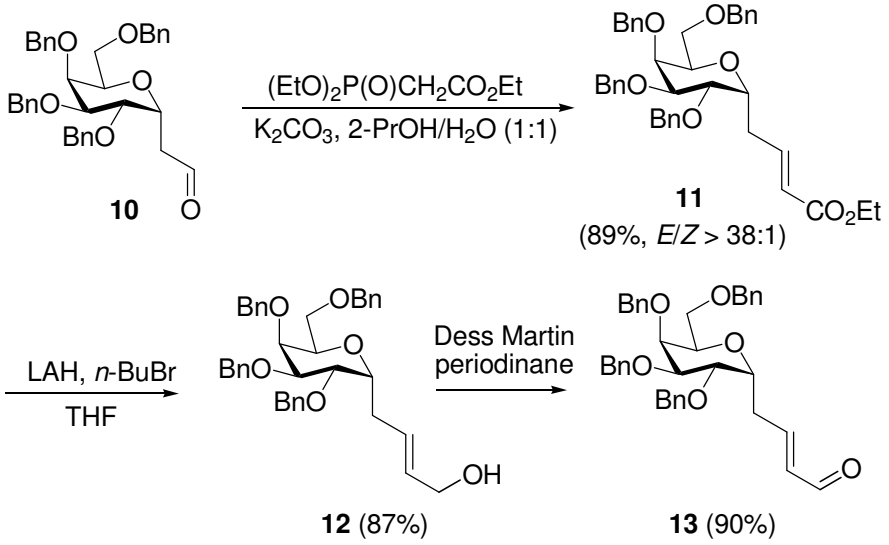


3.3 Results and Discussion

Improved Synthesis of Allylic Alcohol 12 via HWE Reaction and AlH_3 Reduction. Despite the efficiency of the original route, we found that the

preparation of intermediate **12** was not particularly amenable to reaction scale-up. The first task was to modify our synthesis of **12** to allow for the facile preparation of a larger quantity of **13**, the precursor of the ProPhenol-catalyzed asymmetric alkynylation. The two-step HWE olefination and alane reduction protocol described in Chapter 1 was used to prepare up to 6.5 g of allylic alcohol **12**.[13] Oxidation of **12** with Dess-Martin periodinane gave aldehyde **13** in 90% yield.

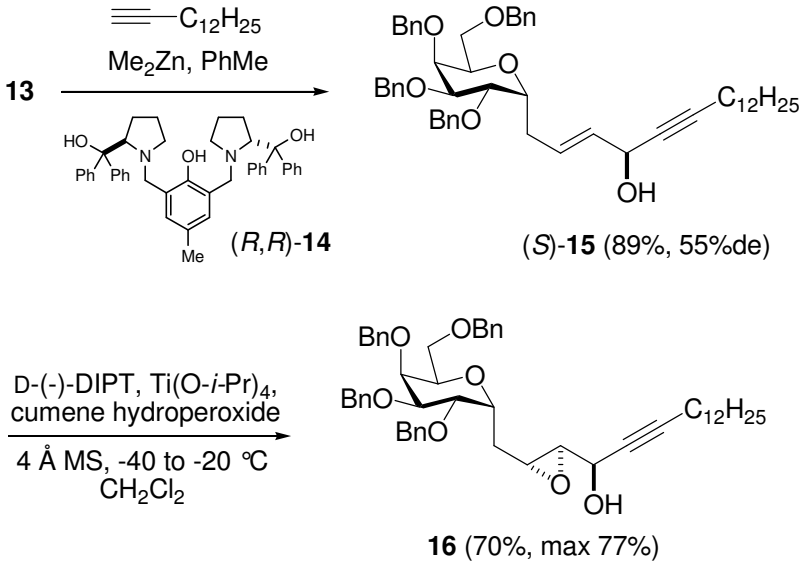
Scheme 3.2 Improved Synthesis of **3**



Asymmetric Synthesis of Allylic Propargylic Alcohol (*S*)-15. As previously reported, the defining transformation of the synthesis of **3** involved the use of the Sharpless kinetic resolution[14] as the key step, which allowed building the three contiguous stereogenic centers in the phytosphingosine moiety. An inherent disadvantage of kinetic resolution is that the maximum yield of this step is 50%. An epimeric mixture (1:1) of allylic propargylic alcohols was used previously,[10] but it would be much more efficient if one could prepare the requisite allylic propargylic

alcohol epimer to participate in the SAE. The ProPhenol-catalyzed asymmetric alkynylation[15] allowed us to prepare the desired allylic propargylic alcohol (*S*)-**15** in 89% yield and 55% de. The *de* and absolute configuration of allylic propargylic alcohols (*S*)-**15** was determined by preparing the (*R*)- and (*S*)-Mosher esters and analyzing their ^{1}H NMR spectra by the subtraction protocol of the advanced Mosher method (Scheme 3.4 and Figure 3.2).[16] Use of these allylic propargylic alcohols of high *de* value improved the yield of **16** up to 70% versus 40% in the previous synthesis[10] employing the Sharpless kinetic resolution on an 1:1 mixture of epimeric allylic propargylic alcohols.

Scheme 3.3 Improved Synthetic Route to Epoxy Alcohol **16** via ProPhenol-Catalyzed Asymmetric Alkynylation



Scheme 3.4 Conversion of (*S*)-**15** to (*S*)- and (*R*)-**19**

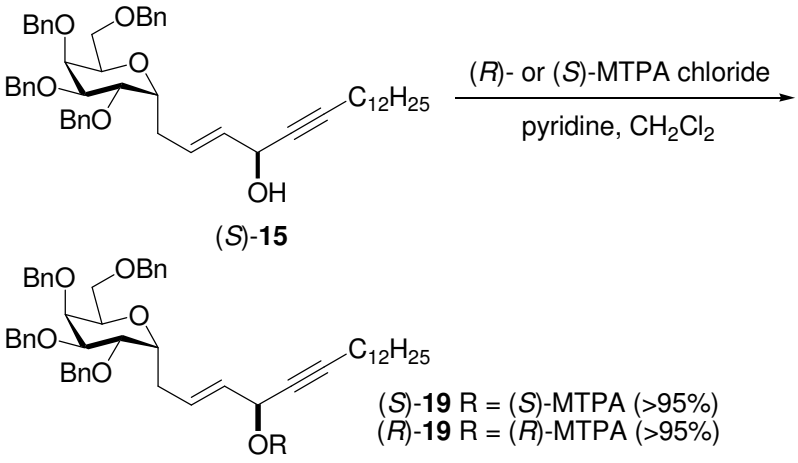
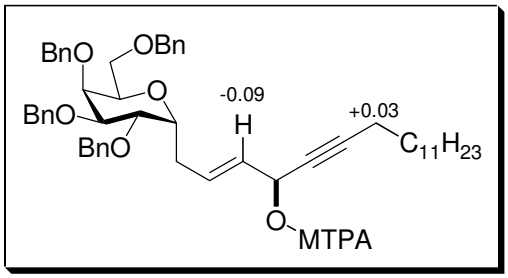


Figure 3.2 Absolute stereochemistry determination of **13** via the advanced Mosher method

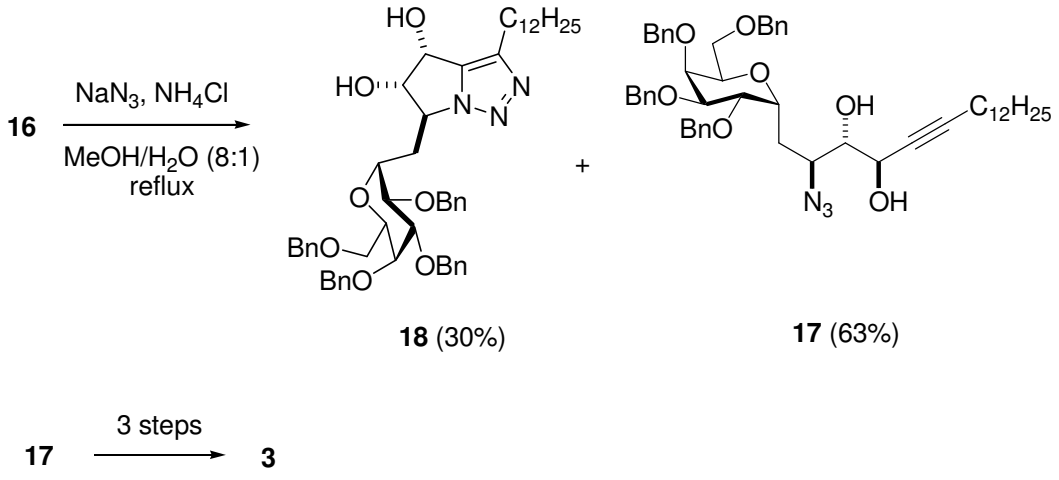


Caption to Fig. 1: $\Delta\delta$ values for the MTPA derivatives (*S*)-**19** and (*R*)-**19** ($\Delta\delta = \delta_S - \delta_R$ ppm, 500 MHz).

Opening of Propargylic Epoxy Alcohol 16 with Azide Nucleophiles. Opening of epoxide **16** by NaN_3/NH_4Cl is not a rapid reaction, requiring extended reaction time in refluxing $MeOH/H_2O$ (8:1). In addition, the extended reflux time led to the formation of bicyclic triazole **18** (30%) as a side product via an intramolecular click reaction,[12] which markedly lowered the yield of the desired

product (Scheme 3.5). The R_f values of the reactant **16** and product **17** were almost the same, making it difficult to judge the consumption of epoxy alcohol **9**. Since bicyclic triazole **18** was formed before the complete consumption of reactant, it is difficult to determine the reaction time at which the desired product azido diol **17** can be obtained as the only product. Therefore, we adopted the $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ conditions described by Sharpless et al.,[17] which was reported to proceed in a short reaction time (15 to 30 min) and high regioselectivity of epoxide opening at the C-3 position. Furthermore, given the unexpected phenomenon reported by Pu and Franck,[9c] we were also interested in determining whether the same product would be obtained compared with the NaN_3/NH_4Cl opening method. To our surprise, treatment of epoxy alcohol **16** with $Ti(O\text{-}i\text{-}Pr)_2(N_3)_2$ gave conjugated aldehyde **20** in 35% isolated yield (16% of **16** was recovered), together with unidentified products (Scheme 3.6). The determination of its structure was based on COSY, HMQC, and NOESY. In the NOESY spectrum (Figure 3.3), strong correlation between the vinyl proton and aldehyde proton clearly demonstrated that the alkene has the *E* configuration. Its formation might arise via a Ti-catalyzed semi-pinacol rearrangement of α-hydroxy epoxides.[18]

Scheme 3.5 Opening of Epoxide **16**



Scheme 3.6 Ti-catalyzed Semi-pinacol Rearrangement of α-Hydroxy Epoxide **16**

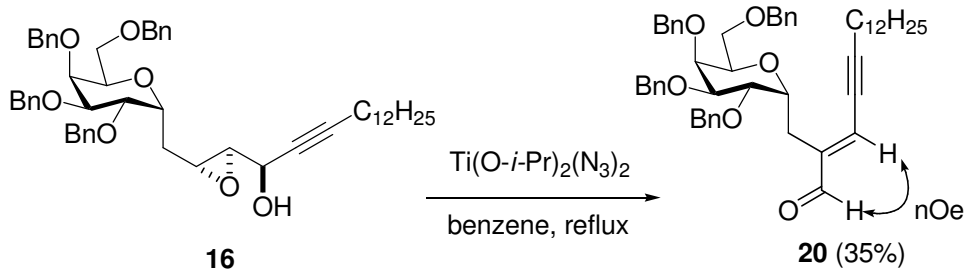
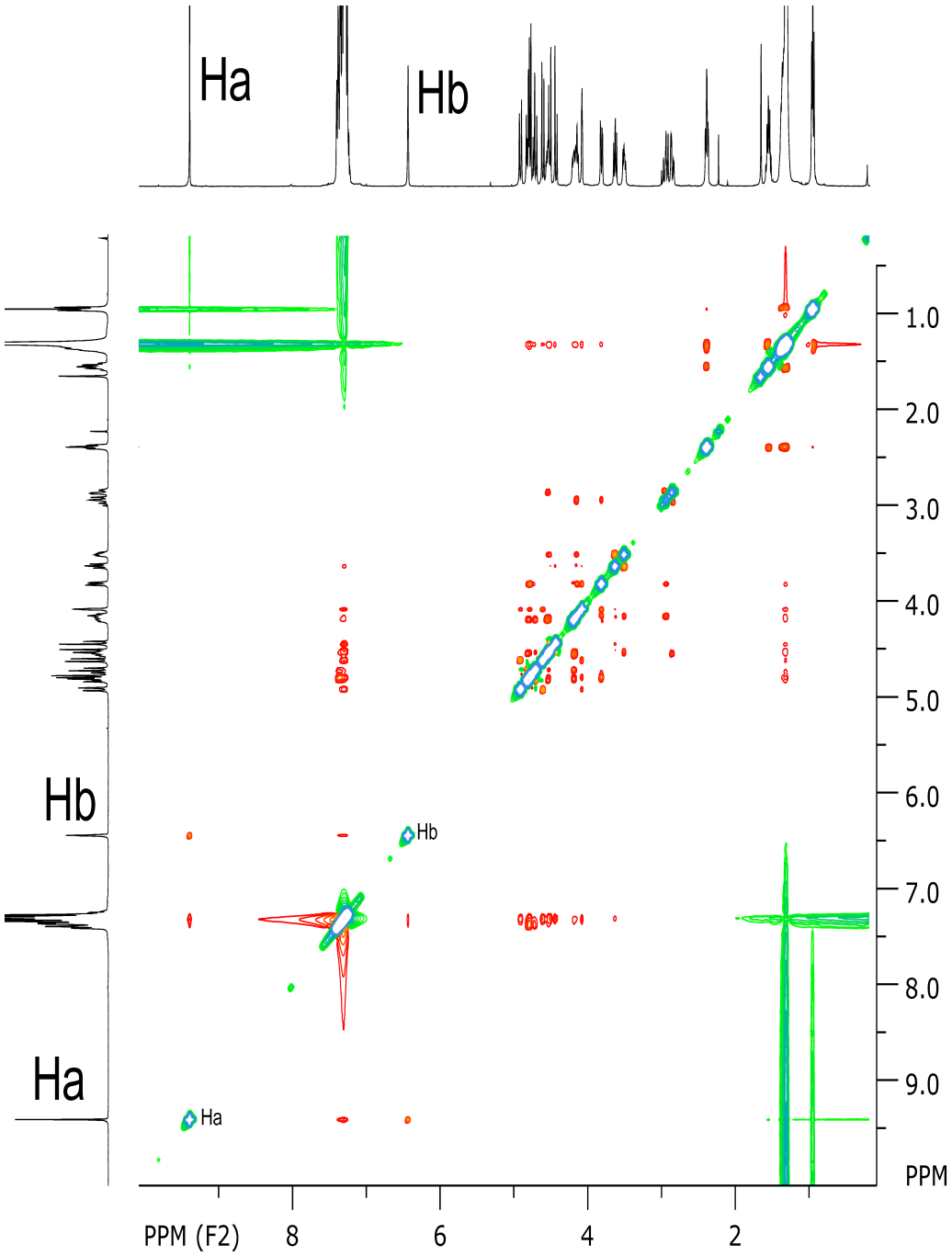


Figure 3.3 NOESY spectrum of **20**

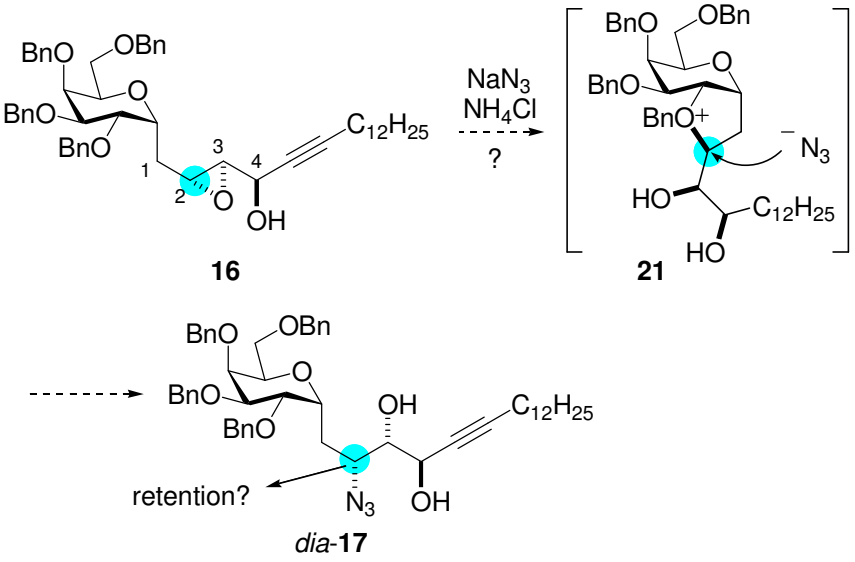


Investigation of the Regiochemistry of Epoxide Opening via Intramolecular Click Reaction. The regioselectivity of opening of epoxide **16** has

already been verified by converting diol **17** into the corresponding isopropylidene acetal to analyze the ^{13}C-NMR chemical shift of the acetal carbon.[10] This evidence can only support the generation of a 1,2-diol instead of a 1,3-diol, but cannot indicate if a Payne rearrangement[19] is involved in the opening process. The intramolecular click reaction of **17** precludes the generation of other regioisomers via Payne rearrangement.

Investigation of the Stereochemistry of Three Contiguous Stereogenic Centers via an Intramolecular Click Reaction. In 1986, Mootoo and Fraser-Reid found that oxygens present in ethers, esters, and a pyranose ring participate efficiently in electrophilic reactions at remote centers, leading to five- and six-membered heterocycles.[20] As shown in Scheme 3.7, we examined whether intramolecular participation by the 2'-*O*-benzyl group formed oxonium ion **21**, which could deliver an azide to form *dia*-**17** with retention configuration. Although the absolute configuration of the N_3-bearing carbon can be determined by the advanced Mosher method, the preparation of the corresponding MTPA amides needs a three-step derivatization: protection of the two hydroxy groups, reduction of the azide to amine, and amide formation. In addition, the important protons around MTPA amides might overlap, making the analysis inconclusive.

Scheme 3.7 Possible Retention Pathway in Opening of Epoxide **16**



Investigation of *J* Values. Inspired by the formation of bicyclic triazole **18**, the by-product of the ring opening of **16** (Scheme 3.8) via an intramolecular click reaction, we decided to determine if coupling constants in a cyclic system can be used to reveal the relative configurations of the three contiguous stereogenic centers. Because the H-4, H-5, and H-6 protons in the ^{1}H NMR spectra overlapped with protons of the galactosyl moiety, we converted **18** to diacetate **23** to better analyze the corresponding coupling constants. Also, in order to compare the configurations of **17** and **18**, diol **17** was converted to its diacetate and then subjected to an intramolecular click reaction in toluene at reflux overnight to give **23** in quantitative yield (Scheme 3.8).

Scheme 3.8 Intramolecular Click Reaction of **17**

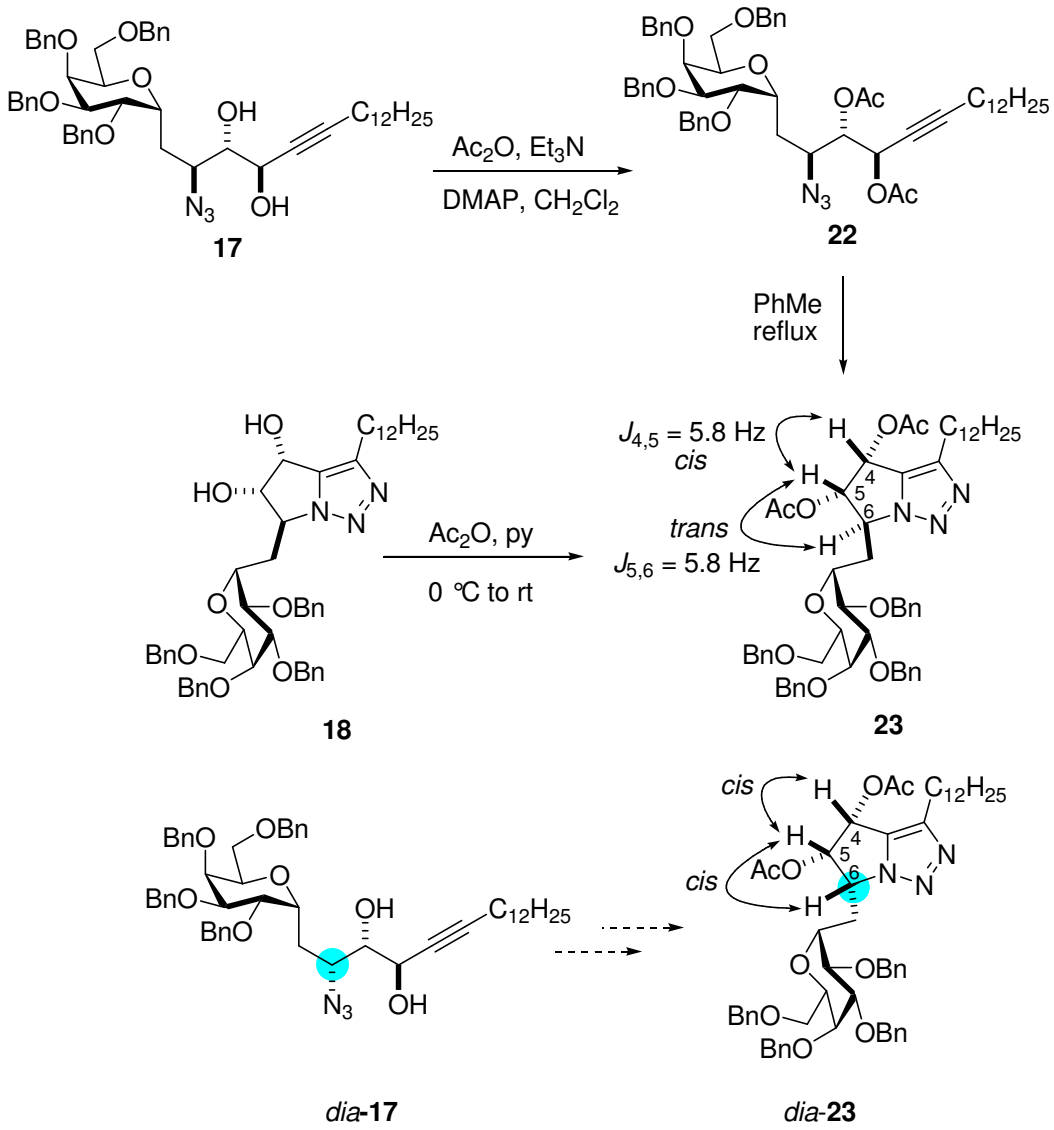
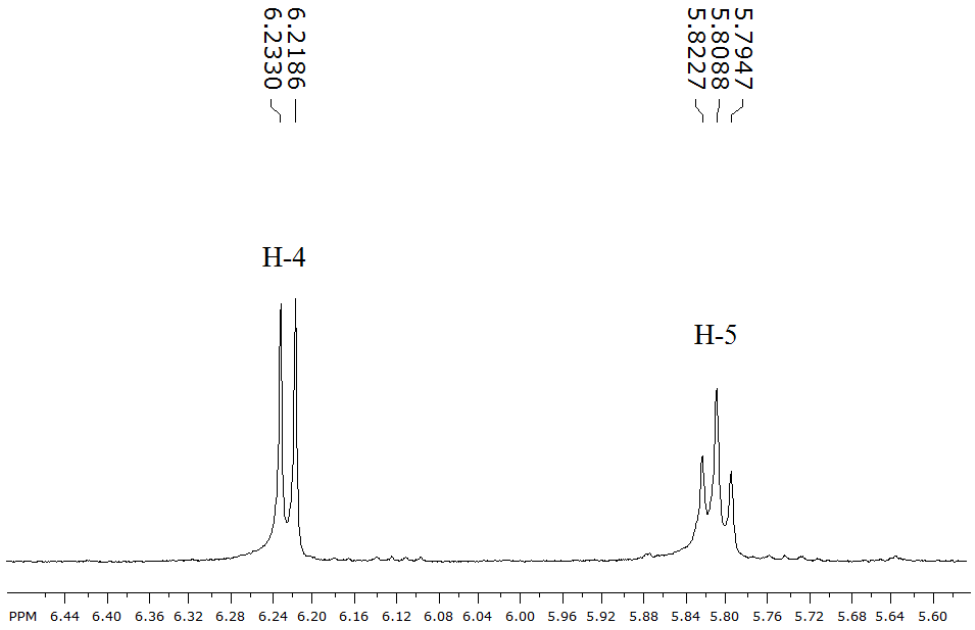
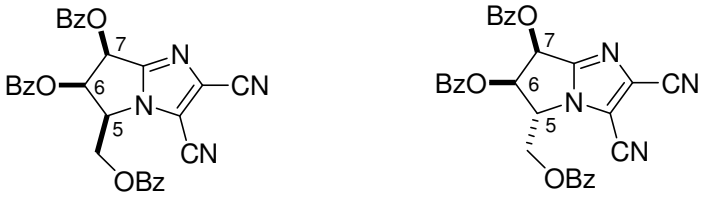


Figure 3.4 Partial ^{1}H NMR spectrum of **23**



As discussed in Chapter 2, the two *J* values in bicyclic triazole **23** are very similar: *cis* $J_{4,5}$ = 5.8 Hz and *trans* $J_{5,6}$ = 5.6 Hz, so that H-5 displayed a triplet signal, thereby mismatching the reported data in the bicyclic system (Figure 3.5).[22] Consequently, if the opening of epoxide **16** proceeded with *retention*, giving rise to *dia*-**17**, and intramolecular click reaction of *dia*-**17** gave bicyclic triazole *dia*-**23**, both *cis* H-4/H-5 and *cis* H-5/H-6 would show the similar *J* values recorded (Scheme 3.8).

Figure 3.5 Reported coupling constants in a structurally similar bicyclic system



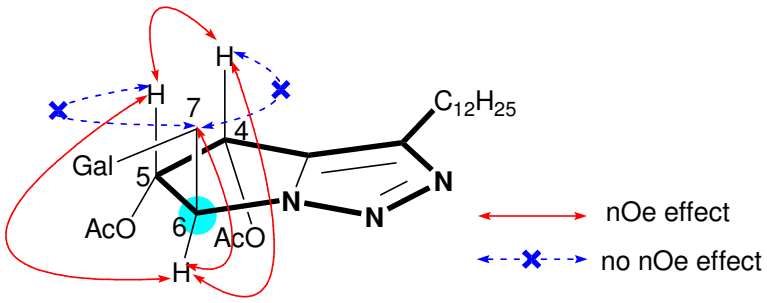
24 **25**

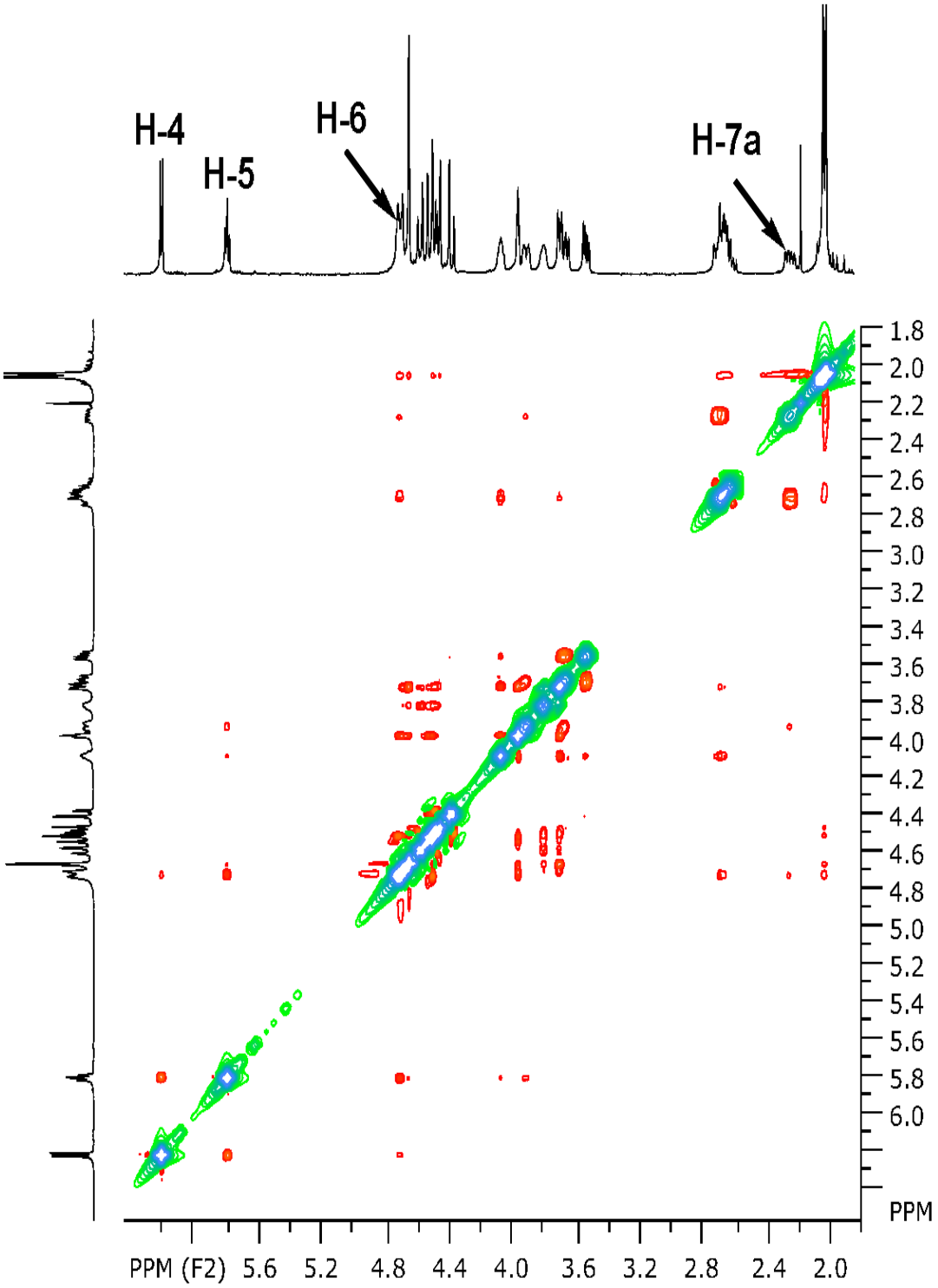
$J_{6,7}$ = 6.0 Hz
$J_{5,6}$ = 7.2 Hz

$J_{6,7}$ = 6.0 Hz
$J_{5,6}$ = 1.8 Hz

nOe Investigation. Initially, we expected that the investigation of the nOe effect in **23** could clarify the stereochemical problem. As shown in Figure 3.6, H-4 and H-7, the two protons putatively on the same side of the bicyclic ring, based on the *J* values, demonstrate no nOe effect, while H-4 and H-6, the two protons on the opposite sides, did show the nOe effect. In addition, we did not observe the nOe effect between the same face protons, H-7 and H-5. Thus, again, it appears that opening of epoxide **16** took place with retention to form, ultimately, *dia*-**23** instead of **23**. However, because H-6 partly overlapped with other protons, the nOe investigation was not reliable as a means for configurational assignment.

Figure 3.6 nOe investigation of **23**

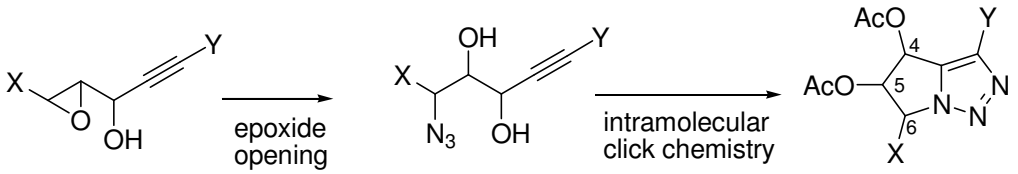


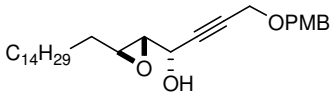
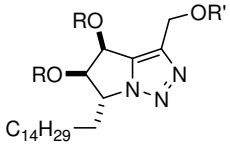
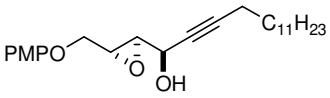
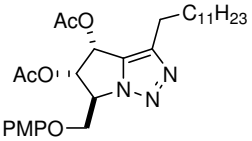
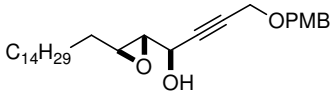
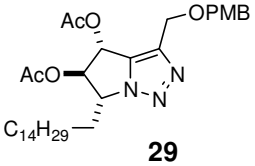
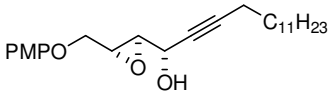
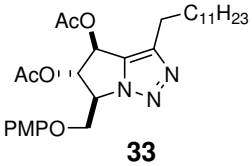


Model Compound Investigation. We then decided to investigate the corresponding *J* values of several simpler compounds. The epoxy alcohols and

bicyclic triazoles shown in Table 3.1 were synthesized by the same sequence we used to prepare **16** and **23**. As predicted, the intramolecular click reaction of *cis* epoxy alcohols **28** and **32** delivered bicylic triazoles **29** and **33** with almost the same *J* value (*trans* $J_{4,\ 5}$ versus *trans* $J_{5,\ 6}$). However, like its sugar counterpart **16**, reaction of *trans* epoxy alcohols **26** and **30** still afforded bicyclic triazoles **27** and **31** with two similar *J* values (disregarding cis between H-4 and H-5 and *trans* between H-5 and H-6). Because the model compounds **27** and **31** gave the same pattern of coupling constants as **23**, these data indicate that if retention indeed occurred, intramolecular 2'-*O*-benzyl participation would not be the reason.

Table 3.1 Use of a model system to investigate relative configurations



Entry	Epoxy Alcohol	Bicyclic Triazole	H-4 Split, *J* (Hz)	H-5 Split, *J* (Hz)
1	 **26**	 **27a** R = Ac, R' = PMB **27b** R = R' = *p*-nitrobenzoyl	**27a** d, 5.6 **27b** d, 5.7	t, 5.8 t, 5.9
2	 **30**	 **31**	d, 5.8	dd, 5.8, 4.4
3	**16**	**23**	d, 5.8	t, 5.6
4	 **28**	 **29**	d, 1.4	t, 1.7
5	 **32**	 **33**	d, 1.3	dd, 1.5, 1.9

Based on the analysis of the *J* values of bicyclic triazole **23** and model compounds (Table 3.1), it is possible that one of the known stereocontrolled steps from allylic propargylic alcohol to azido diol, such as from (*S*)-**15** to **17**, did not proceed in the normal way. Therefore, we need to verify the course of the construction of the three contiguous stereogenic centers as described in Chapter 2 by the advanced Mosher method.

Because the chemical shifts of the important protons in the MTPA esters or amides may overlap with protons of the sugar, the reaction sequence to prepare **31** was selected to verify the stereochemical construction, because these intermediates are structurally simple, and more importantly, it can be converted to D-*ribo*-phytosphingosine.[22] Therefore, once the stereochemical construction of **31** was confirmed, the verification of relative stereochemistry of **23** (thereby **17**) could be achieved. As discussed in Chapter 2, all of the steps of the stereochemical construction of **31** took place in a normal way, and as a result the stereoselective synthesis of α-1*C*-GalCer (**3**) proceeded normally without any intramolecular participation.

3.4 Conclusion

An improved synthetic route to **3** was developed, which included the use a two-step HWE/AlH_3 reduction protocol and ProPhenol-catalyzed asymmetric alkynylation. In order to preclude the possible intramolecular participation by the 2'-*O*-benzyl group during the opening of epoxide **16**, verification of the construction of three contiguous stereogenic centers in the phytosphingosine moiety was explored

with bicyclic triazole **23**, which was formed by an intramolecular click reaction and acetylation of azido diol **17**. However, the stereochemical assignments based on the coupling constants of **23** were inconclusive. According to the systematical investigation of the model compound **31** described in Chapter 2, the epoxide-opening of **16** did indeed proceed with inversion, thus excluding intramolecular participation by the 2'-*O*-benzyl group. These results underscore the need for caution when coupling constants alone are used to judge the relative configuration in bicyclic triazoles and related systems.

3.5 Experimental Section

Allylic Propargylic Alcohol (*S*)-15. A flame-dried 100-mL round-bottom flask was charged with commercially available ProPhenol ligand (*R*,*R*)-**14** (123 mg, 0.192 mmol), 1-tetradecyne (1.12 g, 5.76 mmol), and 25 mL of toluene. The solution was degassed by two freeze-pump-thaw cycles and filled with N_2. A solution of Me_2Zn (4.8 mL, 1.2 M in toluene, 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 **13** (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 ^{o}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. Purification of the

residue by flash chromatography (hexane/EtOAc 7:2) provided (*S*)-**15** (1.35 g, 89%, 55% *de*). The *de* and absolute configuration of (*S*)-**15** were determined by analysis of its corresponding (*S*)- and (*R*)-MTPA esters, (*S*)-**19** and (*R*)-**19**, respectively, which were prepared as described in Chapter 2 (page 42). For data of (*S*)-**15**: ^{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.

Epoxy Alcohol (16) and Azido Diol 17. The preparation of **16** and **17** was according to Ref. 10, and the ^{1}H and ^{13}C NMR spectra of **17** matched the data reported in Ref. 10.

Bicyclic Triazole Diol 18. This compound was obtained as a side product (35% yield) during the opening of epoxide **16**. ^{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.

Azido Diol Diacetate 22. To a solution of 29 mg (34 μmol) of **17** in 2 mL of dry pyridine was added 0.5 mL (5.30 mmol) of Ac_2O at 0 °C. 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 amount of CH_2Cl_2, and filtered through a pad of silica gel in a buret. The pad was rinsed with 10 mL of hexane/EtOAc 3:1. Concentration gave diacetate **22** (30 mg, 95%) 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, 1), 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.

Bicyclic Triazole Diol Diacetate 23. This compound was prepared from **18**. To a solution of 17 mg (20 μmol) of **18** in 2 mL of dry pyridine was added 0.5 mL (5.30 mmol) of Ac_2O at 0 °C. 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 amount of CH_2Cl_2, and filtered through a pad of silica

gel in a buret. The pad was rinsed with 10 mL of hexane/EtOAc 3:1. Concentration gave diacetate **23** (18 mg, 97%) as a colorless syrup.

Compound **23** was also prepared from **22**. The solution of **22** (10 mg, 11 μmol) in 2 mL of toluene was stirred at reflux overnight. After the reaction was cooled to rt, removal of the solvent provided **23** (10 mg, 100%) as a colorless syrup: ^{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.

α,β-Unsaturated Aldehyde 20. 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. A solution of epoxide **16** (160 mg, 0.2 mmol) in anhydrous benzene (5 mL) and was added to the solution in one portion. After the mixture was stirred for 30 min at 80 °C and cooled to rt, the solvent was removed under reduced pressure. Et_2O (20 mL) was added, followed by addition of 5% H_2SO_4 (10 mL, v/v). 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. Flash chromatography

(hexane/EtOAc 7:1) afforded **20** (55 mg, 35% yield) as a yellow oil: ^{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, 194.0; ESI-HRMS $[M+Na]^+$ calcd for *m/z* $C_{52}H_{65}O_6^+$ 785.4776, found 785.4784.

3.6 References and Notes

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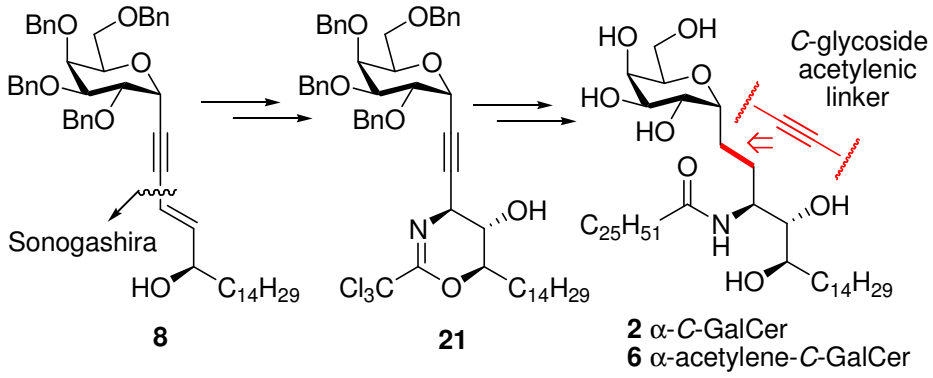
Chapter 4: Synthesis of Immunostimulatory α-*C*-Galactosylceramide Glycolipids via Sonogashira Coupling, Asymmetric Epoxidation, and Trichloroacetimidate-Mediated Epoxide Opening

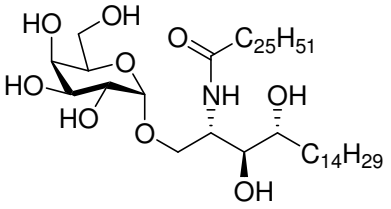
4.1 Abstract

Stereocontrolled syntheses of α-*C*-GalCer (**2**) and its α-*C*-acetylenic analog **6** were accomplished in high efficiency by a convergent construction strategy from 1-hexadecene and D-galactose. The key transformations include Sonogashira coupling, Sharpless asymmetric epoxidation, and Et_2AlCl-catalyzed cyclization of an epoxytrichloroacetimidate to generate protected dihydrooxazine **21**.

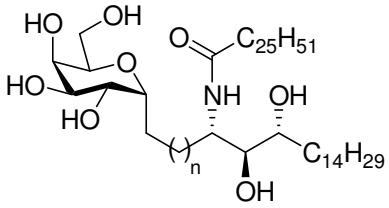


4.2 Introduction

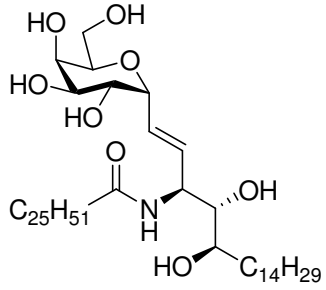
Figure 4.1 Structures of glycolipids **1**-**6**



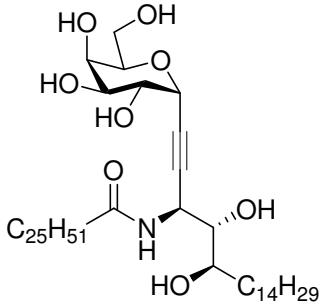
1 α-GalCer (KRN7000)



2 n = 1 α-*C*-GalCer
3 n = 0 α-1*C*-GalCer
4 n = 2



5 GCK127

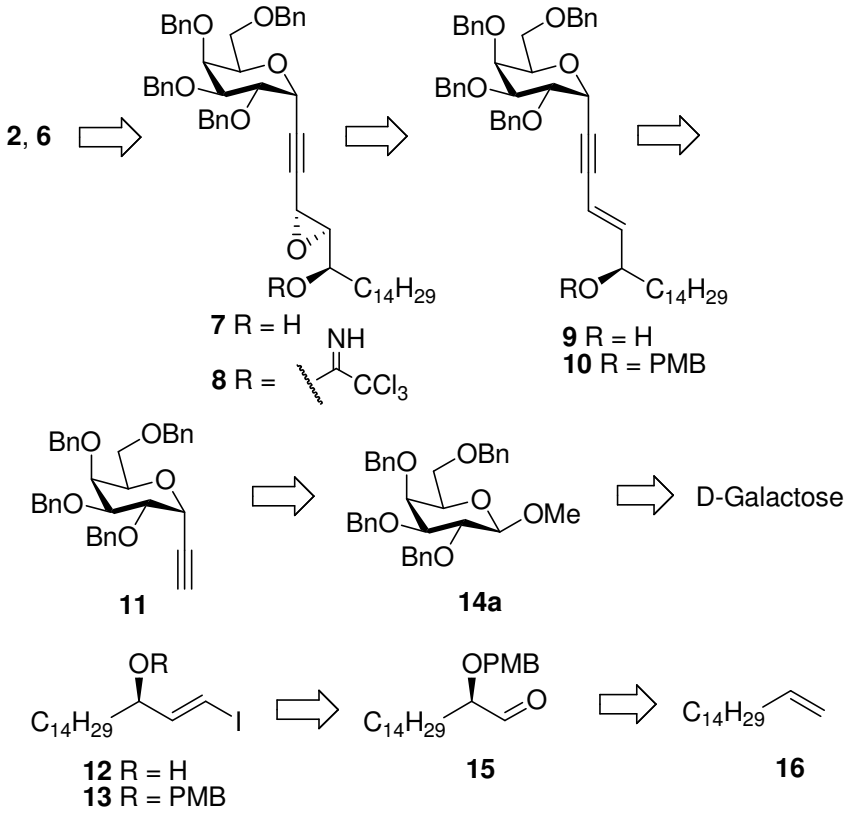


6

As discussed in Chapter 3, KRN7000 (**1**) and its *C*-glycoside analogs (**2**, **3**, **4**, and **5**) provided useful information about SAR with respect to the linker area. In order to make larger quantities of **2** available to the immunology community,[1] diverse synthetic approaches toward this important synthetic target have been developed.[2, 3] However, there remains a need for efficient stereoselective methods for the preparation of **2**. We report a concise convergent synthesis of **2** from readily available, inexpensive starting materials. In addition, the synthetic route to **2** reported here permits modification of the linker region, which appears to be critical

for Th1 vs Th2 selectivity. We also report the synthesis of **6**, which contains an acetylenic moiety in the linker.

Scheme 4.1 Retrosynthetic Plan

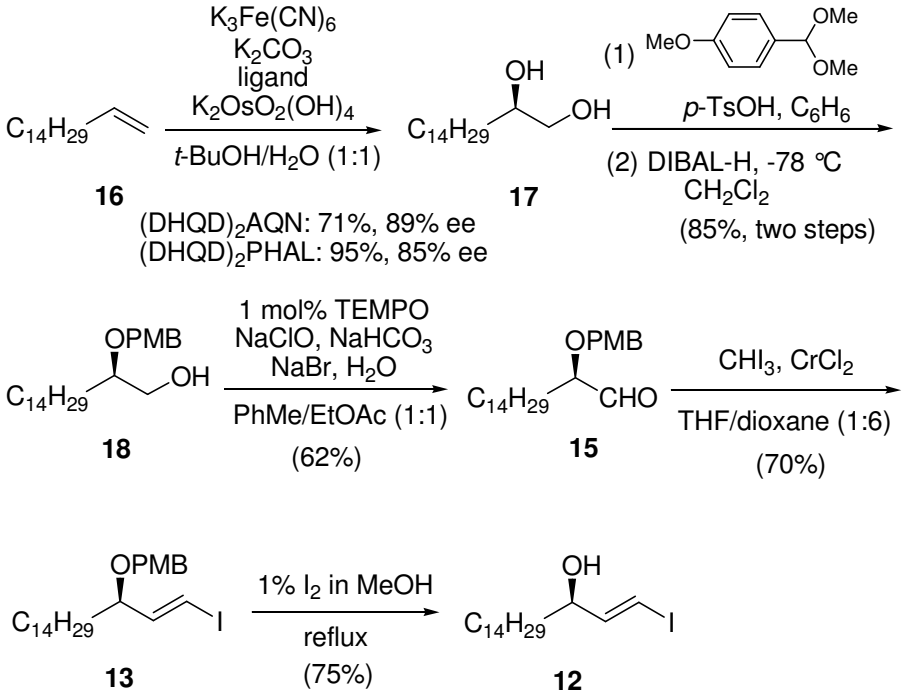


4.3 Results and Discussion

As shown in the retrosynthetic analysis (Scheme 4.1), we envisioned that the three contiguous stereogenic centers in the phytosphingosine moiety can be accessed from epoxy alcohol **7** after reaction with trichloroacetonitrile to give **8**, followed by a Lewis acid catalyzed epoxide opening at the propargylic carbon. The requisite epoxide **7** could be furnished by Sharpless asymmetric epoxidation (SAE)[4] of **9**,

which in turn could be obtained from **10** via Sonogashira cross-coupling[5] between two building blocks, **11** and **12** (or **13**). **11** can be assembled via α-*C*-ethynylation of **14a** (accessible from D-galactose; see Experimental Section), and **12** can be prepared via Takai olefination[6] of aldehyde **15**, which can be made from 1-hexadecene (**16**).

Scheme 4.2 Synthesis of Vinyl Iodide **12**



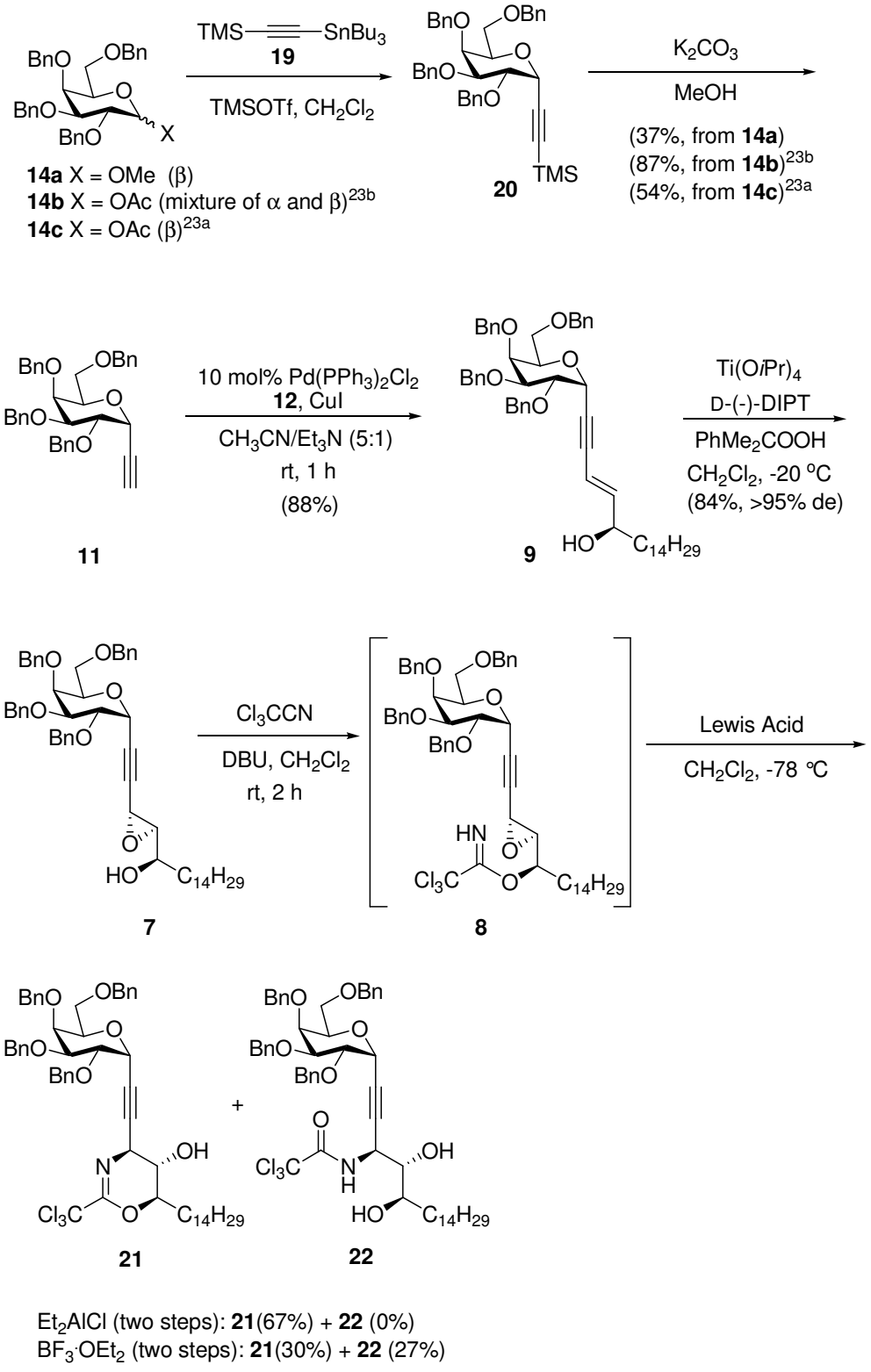
As shown in Scheme 4.2, Sharpless asymmetric dihydroxylation of **16** with AD-mix-β provided the desired diol **17** (85% ee) in almost quantitative yield.[7] Alternatively, the use of the ligand $(DHQD)_2AQN$, which was reported to have a higher enantioselectivity than the PHAL-based ligand in an aliphatic system,[8] delivered **17** in a lower yield (71%) and slightly higher ee value (89% ee). Diol **17** was converted to its *p*-methoxybenzylidene (PMB) acetal, which was reduced with

DIBAL-H to give alcohol **18** (85%, two steps).[9] The use of a protocol with sodium hypochlorite catalyzed by TEMPO[10] gave the desired aldehyde **15** in 62% yield without any erosion of the ee value.[11] Since an (*E*)-l-iodoalkene was required, we used the Takai reaction,[6] which is known to be highly *E* stereoselective. Condensation of aldehyde **15** with iodoform in the presence of chromium(II) chloride yielded the expected (*E*)-vinyl iodide **13** in 70% yield when the Evans modification[12] was used. Deprotection of the PMB group using I_2 in MeOH[13] afforded vinyl iodide **12** (75%).

Initially, α-*C*-ethynylgalactoside **11** was prepared by reaction of 1-acetoxy-2,3,4,6-tetra-*O*-benzyl-D-galacto-pyranoside (**14b**,**c**) with ethynyl precursor **19** in the presence of TMSOTf followed by desilylation of **20**.[14] However, we subsequently found that methyl β-D-galactosylpyranoside (**14a**), which is crystalline, can also react with **19** under the same conditions (Scheme 4.3). This reaction proceeded with very high α-stereoselectivity; no corresponding β-anomer was found by ^{1}H NMR. Its efficiency in the preparation of **11** is comparable to that of acetate **14c**. The two-step yield of **11** from **14c** was 54%.[14a,c] Furthermore, **14c** must be prepared from **14a** in two additional steps (~67% overall yield).[15] Thus our two-step yield of **11** from **14a** (37%) is not only comparable to that from **14c** but also offers the advantage that **14a** can be prepared from the very inexpensive D-galactose as reported in the Experimental Section.

With an efficient synthesis of the two building blocks **11** and **12** established, we directed our efforts toward Sonogashira coupling (Scheme 4.3).[5] An initial trial of cross-coupling [$Pd(PPh_3)_4$, CuI (0.5 equiv), *i*-Pr_2NEt (6 equiv), THF] between PMB-

Scheme 4.3 Synthesis of **22**



Et_2AlCl (two steps): **21**(67%) + **22** (0%)
$BF_3{\cdot}OEt_2$ (two steps): **21**(30%) + **22** (27%)

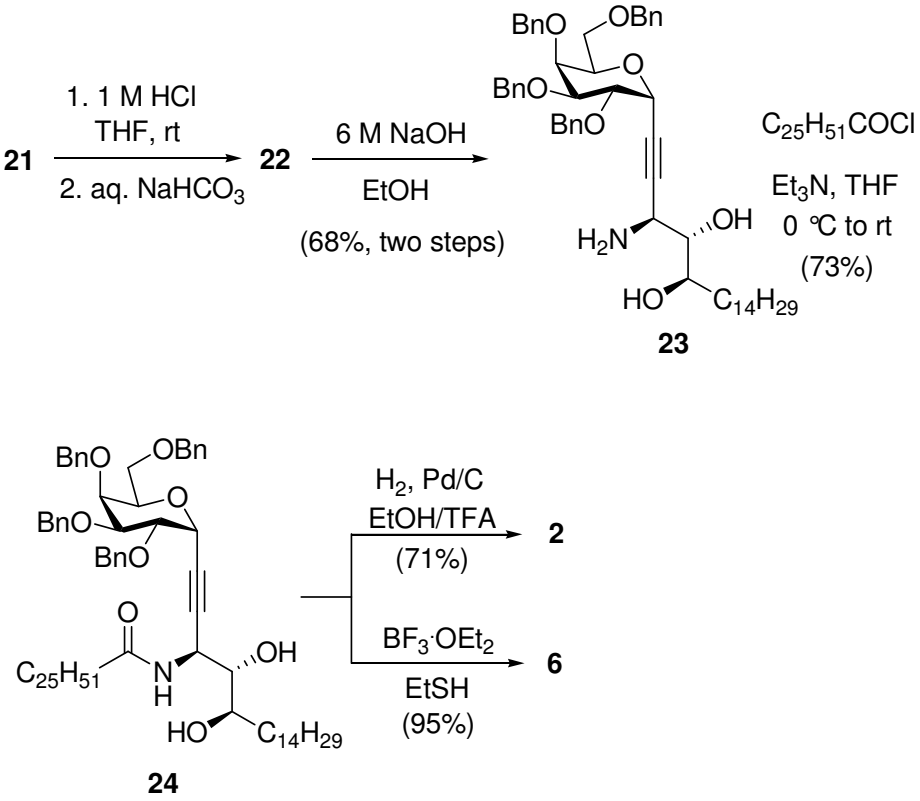
protected alcohol **13** and alkyne **11** in THF provided enyne **10** in 56% yield. During deprotection of the PMB group of **10** with DDQ, the hydroxy group was oxidized to the corresponding ketone. However, when free alcohol **12** was coupled with **10** in the presence of $Pd(Ph_3P)_4$ and CuI in CH_3CN/Et_3N (5:1) the yield of enynol **9** improved to 88%. Use of $Pd(PPh_3)_2Cl_2$ as a precatalyst [$Pd(PPh_3)_2Cl_2$, CuI, CH_3CN/Et_3N (5:1)] afforded **9** in about the same yield as obtained with $Pd(Ph_3P)_4$.

Catalytic or substoichometric SAE of **9** was ineffective, producing little conversion after 20 h at -20 °C. The reaction using 4 equiv of cumene hydroperoxide as the epoxidizing agent catalyzed by 2.5 equiv of $Ti(O\text{-}i\text{-}Pr)_4$ and 2.6 equiv of D-(-)-DIPT provided propargylic epoxy alcohol **7** in high yield (84%) and excellent diastereoselectivity (>95%).[16] Chelation-controlled opening of 2,3-epoxy alcohol **7** with NaN_3 and in the presence of NH_4Cl in aqueous MeOH under reflux failed to provide the desired azido diol, delivering instead a complex mixture.[17] Et_2AlCl-catalyzed cyclization[18] of trichloroacetimidate **8**, prepared by reaction of **7** with 6.0 equiv of trichloroacetonitrile in the presence of 3.5 equiv of DBU,[18d] gave dihydrooxazine **21** in a two-step yield of 67%. It is noteworthy that $BF_3{\cdot}Et_2O$ also catalyzed cyclization of 8 to 21; however, we obtained a mixture of **21** and its hydrolysis product **22** in a ratio of 1:1 (30% vs 27%, respectively).

As shown in Scheme 4.4, acid hydrolysis of **21** provided trichloroacetimide **22**, which was treated with ethanolic NaOH to deliver amine **23** in 68% overall yield. Reaction of amine **23** with hexacosanoyl chloride[3] gave amide **24** in 73% yield. Catalytic hydrogenation (Pd/C, H_2, EtOH/TFA)[19] of the linking triple bonds, together with global removal of the benzyl protecting groups, afforded the target α-

C-glycoside **2**.[20] However, attempted reduction using Pearlman's catalyst [H_2, $Pd(OH)_2$, CH_2Cl_2/MeOH] resulted in incomplete saturation of the acetylenic group. The preparation of $_6$ from $_{24}$ was achieved by $BF_3{\cdot}OEt_2$/EtSH deprotection of the benzyl groups,[21] leaving the acetylenic moiety intact, in almost quantitative yield.

Scheme 4.4 Synthesis of **2** and **6**

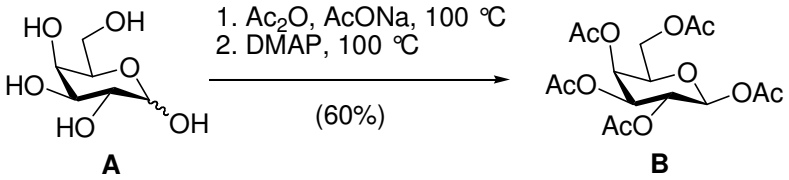


4.4 Conclusion

In conclusion, a convergent and stereoselective synthetic route to α-*C*-GalCer (**2**) and its analog **6** containing an acetylenic linker was accomplished. Notable features include the concise formation of three contiguous stereogenic centers in the

phytosphingosine moiety by Sonogashira cross-coupling followed by Sharpless asymmetric epoxidation and Et_2AlCl-catalyzed cyclization of an epoxytrichloroacetimidate intermediate. This convergent construction from simple starting materials (10 steps from **14a** with 6.5% overall yield) permits the preparation of analogs with variations in the linker area.

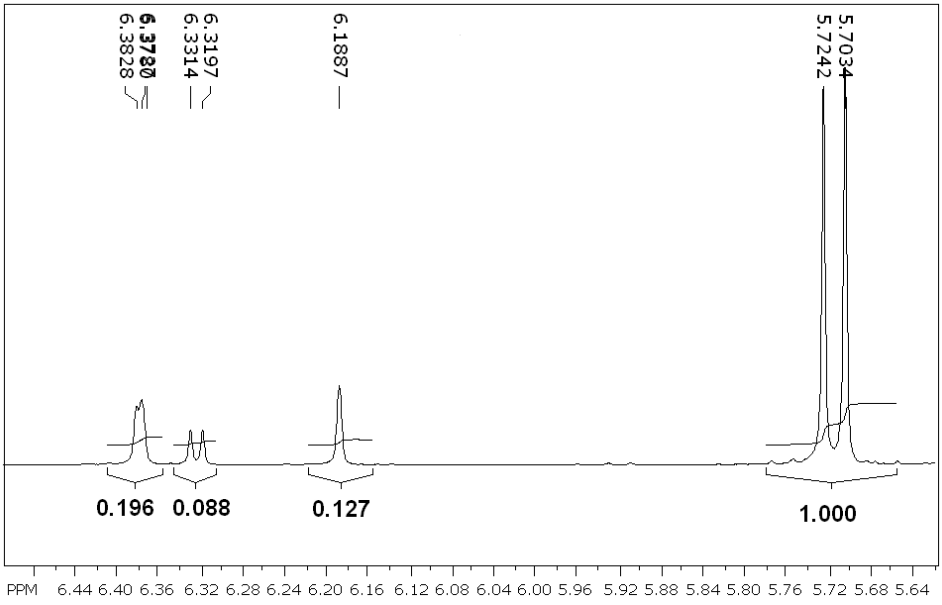
4.5 Experimental Section

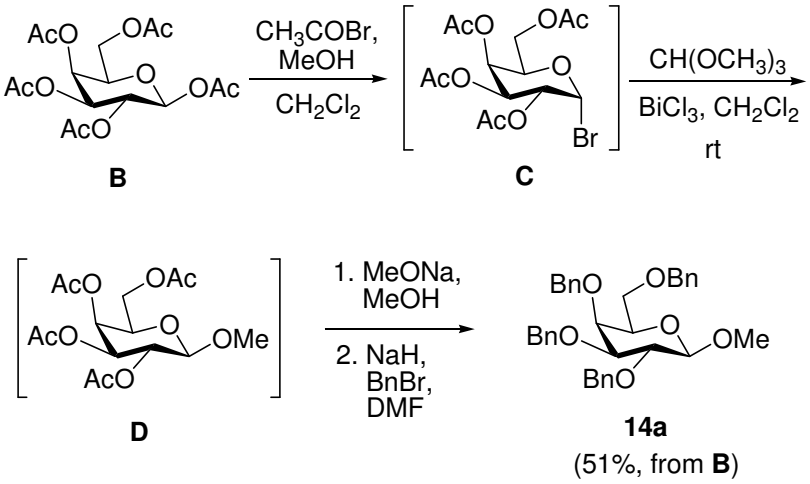


Compound B.[22, 23] A mixture of D-galactose (18.1 g, 0.10 mol) and sodium acetate (825 mg, 10.0 mmol) in 50 mL (0.528 mol) of Ac_2O was heated overnight at 100 °C (oil bath temperature). At this point, TLC showed the incomplete consumption of **A**. After addition of a catalytic amount of DMAP (1.22 g, 10.0 mmol), the mixture was stirred at same temperature and **A** was completely consumed overnight. The reaction mixture was diluted with EtOAc (250 mL) and washed with brine and then with water. The organic layer was dried over Na_2SO_4 and concentrated to give 39.21 g (100%) of an α- and β-mixture of D-galactopyranose pentaacetate and D-galactofuranose pentaacetate (see Figure 4.2). The product was purified by recrystallization from hexane/EtOAc (2:1) to give β-D-galactopyranose pentaacetate **B** (23.5 g, 60%): $[\alpha]^{23.5}_D$ +27.1 (*c* 1.03, $CHCl_3$) [lit.[22h]

$[\alpha]^{20}_{D}$ +25 ($CHCl_3$); lit.[22i] $[\alpha]^{20}_{D}$ +25.2 ($CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.05 (s, 6H), 2.13 (s, 3H), 2.17 (s, 3H), 4.03-4.21 (m, 3H), 5.09 (dd, *J* = 3.4, 10.4 Hz, 1H), 5.30-5.37 (m, 1H), 5.43 (d, *J* = 2.4 Hz, 1H), 5.71 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.48, 20.57, 20.59, 20.75, 61.0, 66.7, 67.7, 70.8, 71.6, 92.1, 168.9, 169.3, 169.9, 170.1, 170.3.

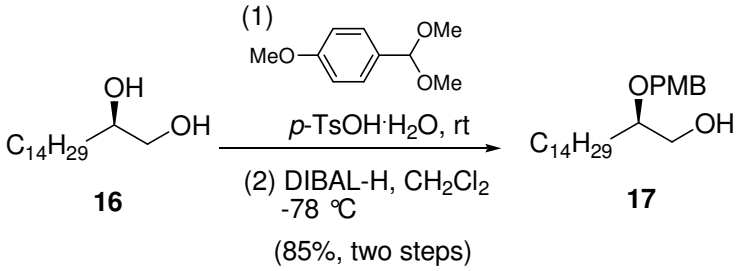
Figure 4.2 Partial ^{1}H NMR spectrum of crude **B.** The signals of the anomeric protons of **B** and the other three isomers (α-D-galactopyranose and α- and β-D-galactofuranose pentaacetates) are shown.





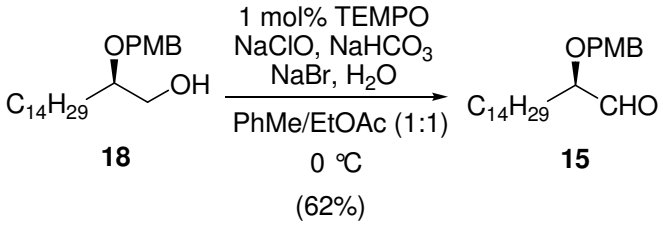
Compound 14a. To a solution of **B** (19.6 g, 50.2 mmol) in 50 mL of CH_2Cl_2 were added acetyl bromide (12 mL, 162 mmol) and MeOH (3.0 mL, 74.1 mmol) at 0 °C. After all of the starting pentaacetate was consumed, the mixture was concentrated to give crude α-D-galactosyl bromide **C**,[24] which was dried under high vacuum overnight. To a stirred solution of **C** and trimethyl orthoformate (10.0 mL, 91.4 mmol) in 50 mL of CH_2Cl_2 was added $BiCl_3$ (3.16 g, 10.0 mmol) at rt.[25] After 5 h, the reaction mixture was diluted with CH_2Cl_2 (100 mL), and washed successively with saturated aqueous $NaHCO_3$ solution and water. After the organic layer was dried (Na_2SO_4) and concentrated, the residue was dried further under vacuum. The crude tetraacetate product **D**[26] was dissolved in 100 mL of anhydrous MeOH and treated with MeONa (5 mL, 30% in MeOH) under reduced pressure in order to remove the methyl acetate formed. After **D** was dried under vacuum, *O*-benzylation was carried out using NaH (10.1 g, 252 mmol; 60% in white oil) and benzyl bromide (30 mL, 252 mmol) in 50 mL of DMF. The product was purified by column chromatography on silica gel (hexane/EtOAc 10:1 to 6:1) followed by

recrystallization from hexane/EtOAc to give methyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranoside **14a**:[27] (14.2 g, 51% overall yield): $[\alpha]^{24.2}_{D}$ -2.4 (*c* 1.08, $CHCl_3$) [lit.[27b] $[\alpha]^{26.6}_{D}$ -0.84 (*c* 0.7, $CHCl_3$)]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.49-3.56 (m, 2H), 3.54 (s, 3H), 3.38-3.60 (m, 2H), 3.80 (dd, 1H, *J* = 2.32, 7.8 Hz), 3.89 (d, 1H, *J* = 2.32), 4.27 (d, 1H, *J* = 7.68 Hz), 4.40 (d, 1H, *J* = 19.2 Hz), 4.45 (d, 1H, *J* = 11.7 Hz), 4.61 (d, 1H, *J* = 11.7 Hz), 4.68-4.77 (m, 3H), 4.89 (d, 1H, *J* = 10.9 Hz), 4.94 (d, 1H, *J* = 11.7 Hz), 7.22-7.37 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.0, 68.8, 72.9, 73.27, 73.5, 74.4, 75.1, 79.6, 82.1, 105.0, 127.47, 127.50, 127.7, 127.8, 127.9, 128.07, 128.10, 128.22, 128.25, 128.30, 128.4, 137.9, 138.4, 138.6, 138.7.



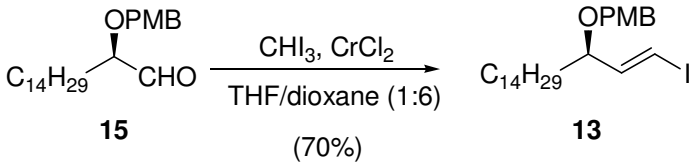
Compound 17. A solution of diol **16** (24.6 g, 95.2 mmol) in benzene (300 mL) was treated with *p*-methoxybenzaldehyde dimethylacetal (37.8 mL, 190 mmol) and *p*-toluenesulfonic acid monohydrate (1.8 g, 9.5 mmol). The reaction mixture was stirred at rt overnight and then concentrated. The residue was used without purification in the next step. The crude acetonide (maximum 95.2 mmol) was dissolved in CH_2Cl_2 (500 mL), cooled to -78 °C, and treated with DIBAL-H (1.0 M in hexane; 333 mL, 333 mmol). After 30 min, the reaction mixture was gradually warmed to rt, quenched with MeOH (10 mL), diluted with Et_2O (700 mL), and

treated with a saturated solution of Rochelle's salt (500 mL). The resultant biphasic mixture was stirred vigorously at rt until the organic phase turned clear. The organic phase was then dried with $MgSO_4$, filtered through Na_2SO_4, and concentrated. Flash chromatography (hexane/EtOAc 3:1) afforded **17** (30.6 g, 85% yield for two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.20-1.40 (m, 24H), 1.43-1.52 (m, 1H), 1.57-1.66 (m, 1H), 2.02 (brs, 1H), 3.45-3.53 (m, 2H), 3.64-3.70 (m, 1H), 3.80 (s, 3H), 4.46 (d, *J* = 11.2 Hz, 1H), 4.56 (d, *J* = 11.2 Hz, 1H), 6.87-6.91 (m, 2H), 7.26-7.29 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.4, 29.3, 29.54, 29.58, 29.63, 29.66, 29.68, 29.8, 30.8, 31.9, 55.2, 64.2, 71.1, 79.4, 113.8, 129.4, 130.5, 159.2; ESI-HRMS $[M+Na]^+$ calcd for *m/z* $C_{24}H_{42}NaO_3^+$ 401.3026, found 401.3023.



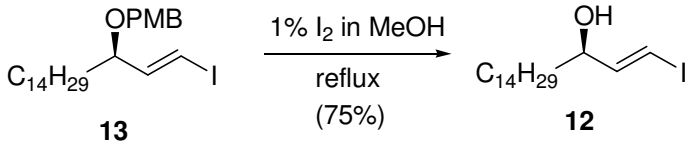
Compound 15. To a solution of 19 g (50.2 mmol) of alcohol **18** in 400 mL of EtOAc/PhMe (1:1) were added a solution of NaBr (10.8 g, 105 mmol in 50 mL H_2O) and TEMPO (235 mg, 1.51 mmol) at 0 °C. Clorox (76 mL) was diluted to 190 mL with H_2O and buffered by the addition of $NaHCO_3$ (12.3 g, 146 mmol). The bleach solution was added dropwise to the reaction flask over 1 h and stirred for an additional 10 min at 0 °C. The ice bath was removed, the reaction mixture was diluted with 800 mL of EtOAc, and the layers were separated. The organic layer

was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to yield **15** (11.8 g, 62%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.20-1.46 (m, 24H), 1.61-1.68 (m, 2H), 3.70-3.75 (m, 1H), 3.81 (s, 3H), 4.48 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 11.2 Hz, 1H), 6.86-6.91 (m, 2H), 7.25-7.30 (m, 2H), 9.61 (d, *J* = 2.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 24.7, 29.34, 29.37, 29.51, 29.59, 29.63, 29.65, 29.66, 30.0, 31.9, 55.2, 72.2, 83.1, 113.8, 129.3, 129.7, 159.4, 204.2; ESI-HRMS $[M+NH_4]^+$ calcd for *m/z* $C_{24}H_{44}NO_3^+$ 394.3316, found 394.3302.

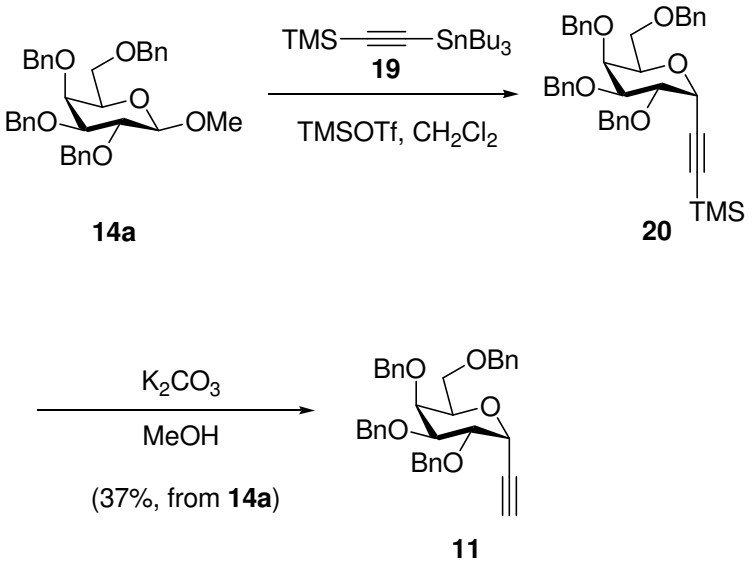


Compound 13. To a slurry of anhydrous chromium(II) chloride (27.5 g, 224 mmol) in THF (60 mL) was added a solution containing **15** (8.40 g, 22.3 mmol) and iodoform (26.3 g, 66.9 mmol) in dioxane (360 mL). The resulting brown suspension was stirred at rt overnight, and then was diluted with Et_2O (600 mL) and poured into 200 mL of water. The aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Purification of the crude product by flash chromatography (hexanes/EtOAc 40:1) afforded iodide **13** (7.81 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.17-1.40 (m, 24H), 1.42-1.51 (m, 1H), 1.55-1.65 (m, 1H), 3.66-3.72 (m, 1H), 3.79 (s, 3H), 4.27 (d, *J* = 11.4 Hz, 1H), 4.51 (d, *J* = 11.2 Hz, 1H), 6.26 (d, *J* = 14.6 Hz, 1H), 6.45 (dd, *J* = 7.8, 14.6 Hz, 1H), 6.85-6.89 (m,

2H), 7.21-7.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.1, 29.3, 29.40, 29.49, 29.56, 29.61, 29.63, 29.66, 31.9, 34.9, 55.2, 70.0, 77.8, 81.0, 113.7, 129.3, 130.2, 147.2, 159.1; ESI-HRMS $[M+Na]^+$ calcd for *m/z* $C_{25}H_{41}INaO_2^+$ 523.2043, found 523.2042.

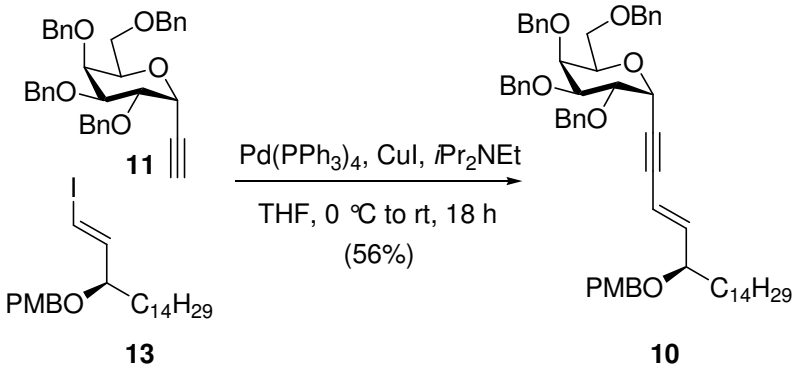


Compound 12. A solution of **13** (8.00 g, 16.0 mmol) in 200 mL of 1% I_2/MeOH (w/v) was heated at reflux for 2 h. After the reaction mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc (200 mL) and washed with saturated aqueous $Na_2S_2O_3$ solution (50 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (hexanes/EtOAc 10:1) to give **12** (4.56 g, 75%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.20-1.40 (m, 24H), 1.49-1.57 (m, 2H), 4.07-4.13 (m, 1H), 6.35 (dd, *J* = 1.1, 14.4 Hz, 1H), 6.58 (dd, *J* = 6.4, 14.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.1, 29.35, 29.42, 29.51, 29.55, 29.62, 29.64, 29.67, 31.9, 36.6, 74.7, 77.1, 148.7; ESI-HRMS $[M+Na]^+$ calcd for *m/z* $C_{17}H_{33}INaO^+$ 403.1468, found 403.1460.



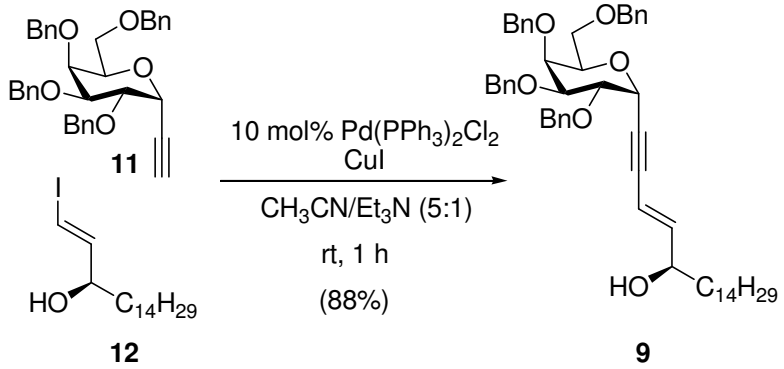
Compound 11.[14] To a solution of **14a** (3.52 g, 6.35 mmol) in CH_2Cl_2 (100 mL) were added tributylstannyl(trimethylsilyl)ethyne **19** (5.49 g, 14.2 mmol) and TMSOTf (2.30 mL, 12.7 mmol) at rt. After the reaction mixture was stirred at rt for 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (30 mL). The product was extracted with EtOAc (3×100 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 20:1) to afford **20** (2.02 g, 3.25 mmol) containing a small amount of stannane. The crude product was dissolved in MeOH (100 mL) and treated with K_2CO_3 (2.0 g) at rt for 4 h. The reaction was quenched with saturated aqueous NH_4Cl solution (30 mL), and extracted with EtOAc (3×100 mL). The combined organic extracts were washed with H_2O and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash column chromatography (hexanes/EtOAc 8:1) to afford α-*C*-ethynylgalactose **11** (1.30 g, 37% two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.53 (d,

J = 2.3 Hz, 1H), 3.48-3.56 (m, 2H), 3.89 (dd, J = 2.8, 9.9 Hz, 1H), 3.97-3.99 (m, 1H), 4.07-4.15 (m, 2H), 4.40 (d, J = 11.7 Hz, 1H), 4.48 (d, J = 11.7 Hz, 1H), 4.57 (d, J = 11.3 Hz, 1H), 4.71-4.81 (m, 4H), 4.86 (d, J = 11.7 Hz, 1H), 4.94 (d, J = 11.3 Hz, 1H), 7.23-7.41 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 67.3, 68.7, 72.6, 73.2, 73.3, 73.5, 74.8, 74.9, 75.1, 76.3, 78.9, 80.2, 127.4, 127.5, 127.6, 127.7, 127.9, 128.22, 128.27, 128.35, 128.36, 128.38, 137.9, 138.2, 138.5, 138.7.



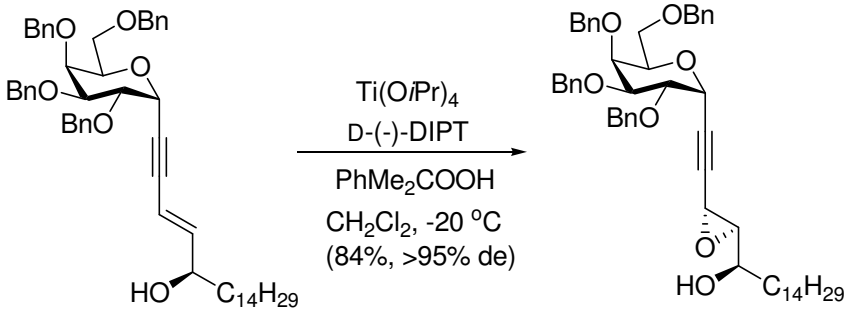
Compound 10. Compounds **11** (150 mg, 0.273 mmol) and **13** (164 mg, 0.328 mmol) were dissolved in THF (5 mL). The solution was degassed by two freeze-pump-thaw cycles. $Pd(PPh_3)_4$ (31 mg, 27.3 μmol) and CuI (25 mg, 0.131 mmol) were added, and the mixture was degassed by one freeze-pump-thaw cycle, placed in a 0 °C bath under N_2, and treated with iPr$_2$NEt (285 μL, 1.64 mmol). The reaction was stirred at rt for 18 h, and then was quenched by the addition of half-saturated aqueous NH_4Cl solution and the mixture was extracted twice with Et_2O. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (hexanes/EtOAc 8:1) to afford **10** (140 mg, 56%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 3H), 1.20-1.41 (m, 24H),

1.45-1.53 (m, 1H), 1.58-1.66 (m, 1H), 3.54-3.57 (m, 2H), 3.72-3.77 (m, 1H), 3.78 (s, 3H), 3.89 (dd, *J* = 2.7, 9.9 Hz, 1H), 3.98-4.01 (m, 1H), 4.09-4.16 (m, 2H), 4.27 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.53 (d, *J* = 11.3 Hz, 1H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.71-4.80 (m, 3H), 4.84 (d, *J* = 11.7 Hz, 1H), 4.94 (d, *J* = 11.5 Hz, 1H), 4.96 (dd, *J* = 1.6, 5.7 Hz, 1H), 5.71 (d, *J* = 16.0 Hz, 1H), 6.07 (dd, *J* = 7.4, 16.0 Hz, 1H), 6.85-6.89 (m, 2H), 7.21-7.40 (m, 22H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.3, 29.3, 29.49, 29.52, 29.60, 29.64, 31.9, 35.3, 55.2, 67.8, 68.6, 70.1, 72.5, 72.9, 73.0, 73.4, 74.7, 74.8, 75.5, 78.8, 80.0, 84.7, 86.0, 110.8, 113.7, 127.4, 127.51, 127.59, 127.71, 127.78, 127.9, 128.15, 128.19, 128.25, 128.30, 128.34, 129.3, 130.5, 137.8, 138.3, 138.5, 138.6, 145.2, 159.1; ESI-HRMS $[M+Na]^+$ calcd for *m/z* $C_{61}H_{76}NaO_7^+$ 943.5483, found 943.5488.



Compound 9. A mixture of **11** (870 mg, 1.59 mmol) and **12** (724 mg, 1.90 mmol) was azeotropically dried under reduced pressure with toluene, and then was dissolved in CH_3CN/Et_3N (30 mL, 5:1). The solution was degassed by two freeze-pump-thaw cycles. After $PdCl_2(PPh_3)_2$ (112 mg, 0.16 mmol) and CuI (182 mg, 0.954 mmol) were added, the reaction mixture was stirred at rt for 1 h, quenched

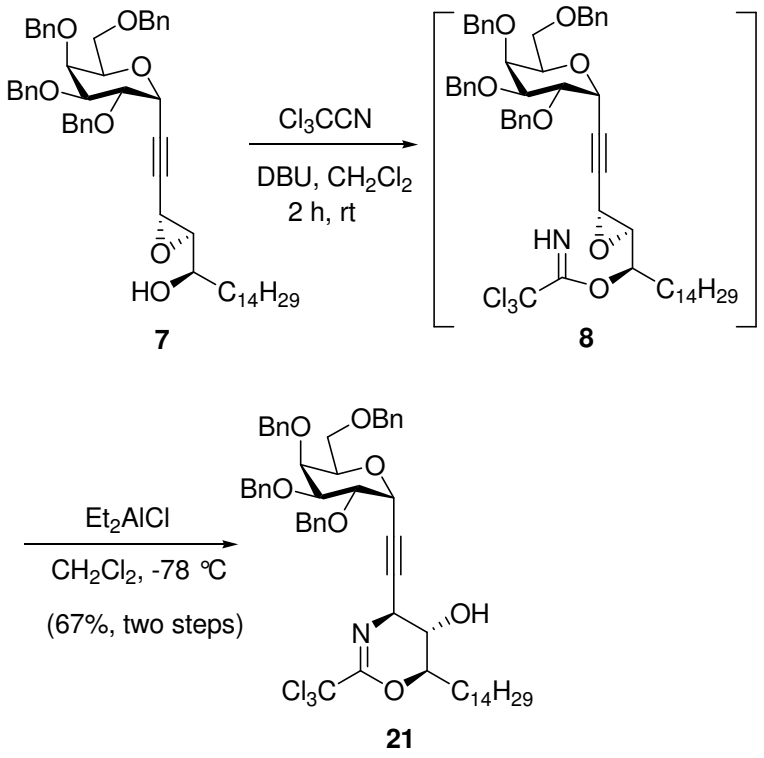
with 0.05 M phosphate buffer (pH 7, 140 mL), and poured into water (250 mL). The product was extracted with EtOAc (3×200 mL). The combined organic layers were dried (Na_2SO_4), and concentrated. Purification by flash chromatography (hexanes/EtOAc 5:1) gave **9** (1.12 g, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.18-1.62 (m, 26H), 3.50-3.56 (m, 2H), 3.86 (dd, *J* = 2.8, 9.8 Hz, 1H), 3.96-4.00 (m, 1H), 4.08-4.12 (m, 2H), 4.13-4.19 (m, 1H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.48 (d, *J* = 11.7 Hz, 1H), 4.57 (d, *J* = 11.4 Hz, 1H), 4.70-4.78 (m, 3H), 4.83 (d, *J* = 11.7 Hz, 1H), 4.91-4.95 (m, 2H), 5.75 (dt, *J* = 15.9, 1.5 Hz, 1H), 6.16 (dd, *J* = 6.1, 15.9 Hz, 1H), 7.22-7.40 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.7, 25.3, 29.4, 29.53, 29.56, 29.62, 29.65, 29.69, 31.9, 36.9, 67.8, 68.7, 72.3, 72.5, 73.0, 73.1, 73.5, 74.7, 74.9, 75.5, 80.0, 84.9, 86.1, 109.2, 127.46, 127.56, 127.62, 127.75, 127.82, 127.9, 128.20, 128.26, 128.30, 128.31, 128.39, 137.9, 138.4, 138.6, 138.7, 146.7; ESI-HRMS $[M+NH_4]^+$ calcd for *m*/*z* $C_{53}H_{72}NO_6^+$ 818.5354, found 818.5351.



9 **7**

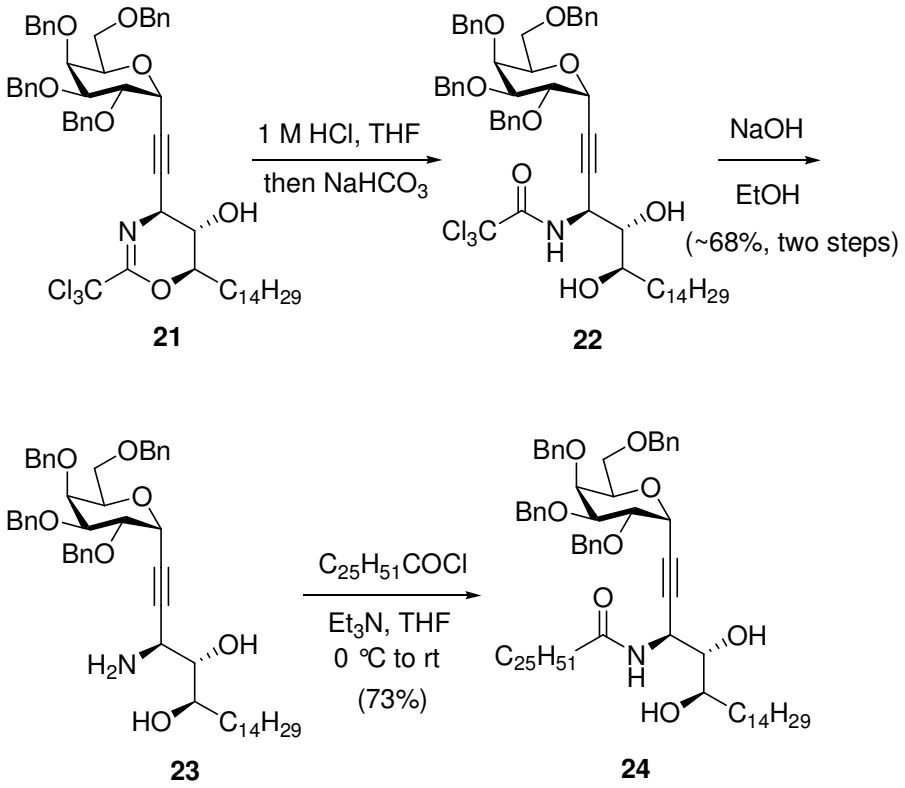
Compound 7. Ti(O-*i*-Pr)$_4$ (887 mg, 3.12 mmol) was added dropwise to a solution of D-(-)-DIPT (761 mg, 3.25 mmol) and 4 Å molecular sieves (1.0 g) in CH_2Cl_2 (30 mL) at -20 °C. After the resultant mixture was allowed to stir at -20 °C

for 50 min, a solution of **9** (1.0 g, 1.25 mmol) in CH_2Cl_2 (10 mL) was added over a period of 15 min. The reaction mixture was allowed to stir at -20 °C for another 30 min, and cumene hydroperoxide (924 μL, 5.00 mmol, 80% technical grade) was added via syringe. The reaction mixture was stirred at -20 °C for an additional 48 h, and 10% aqueous D-tartaric acid (5 mL) was added. The reaction mixture was stirred vigorously at rt for 30 min and filtered through a plug of Celite. The filtrate layers were separated and the aqueous layer was further extracted with CH_2Cl_2 (3×10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc 5:1) afforded epoxide **7** (863 mg, 84%, >95% de; the chiral purity of **7** was determined by analysis of its (*S*)-MTPA ester, see ^{1}H NMR of its (*S*)-MTPA ester, p. S48): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.20-1.62 (m, 26H), 1.85 (d, *J* = 2.5 Hz, 1H), 3.15 (t, *J* = 2.5 Hz, 1H), 3.47-3.56 (m, 3H), 3.78-3.82 (m, 1H), 3.84 (dd, *J* = 2.8, 9.8 Hz, 1H), 3.95-3.98 (m, 1H), 4.03-4.11 (m, 2H), 4.39 (d, *J* = 11.7 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.55 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 12.0 Hz, 1H), 4.73 (d, *J* = 7.6 Hz, 1H), 4.76 (d, *J* = 7.8 Hz, 1H), 4.80-4.85 (m, 2H), 4.91 (d, *J* = 11.3 Hz, 1H), 7.21-7.39 (m, 20H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 25.2, 29.3, 29.49, 29.57, 29.60, 29.64, 31.9, 33.1, 34.5, 41.6, 41.8, 62.4, 67.3, 67.9, 68.5, 72.7, 73.0, 73.4, 74.4, 74.5, 74.8, 75.2, 79.4, 79.9, 84.3, 126.0, 127.42, 127.45, 127.54, 127.6, 127.70, 127.74, 127.9, 128.0, 128.16, 128.20, 128.27, 128.3, 128.7, 128.9, 137.8, 138.2, 138.4, 138.5; ESI-HRMS $[M+NH_4]^+$ calcd for *m*/*z* $C_{53}H_{72}NO_7^+$ 834.5303, found 834.5293.



Compound 21. To a solution of **7** (425 mg, 0.52 mmol) in dry CH_2Cl_2 (10 mL) were added DBU (272 μL, 1.82 mmol) and Cl_3CCN (313 μL, 3.12 mmol). The reaction mixture was stirred at rt for 2 h, and then was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with saturated aqueous NH_4Cl solution, dried (Na_2SO_4), and concentrated. The residue was dissolved in Et_2O and passed through a short column packed with anhydrous Na_2SO_4 and silica gel. Et_2O was evaporated to yield imidate **8** (403 mg) as a light yellow oil, which was dried under high vacuum overnight and used in the next reaction without further purification. To a solution of **8** in CH_2Cl_2 (10 mL) was added Et_2AlCl (1.0 M in hexane, 2.08 mL, 2.08 mmol) at -78 °C. After being stirred at -78 °C for 24 h, the reaction mixture

was diluted with saturated aqueous $NaHCO_3$ solution and the product was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (hexane/EtOAc 4:1) afforded dihydrooxazine **21** (333 mg, 67%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.20-1.64 (m, 25H), 1.85-1.94 (m, 1H), 3.29 (d, *J* = 3.8 Hz, 1H), 3.39-3.47 (m, 2H), 3.53 (dd, *J* = 6.2, 9.4 Hz, 1H), 3.82 (dd, *J* = 2.8, 9.8 Hz, 1H), 3.91-3.95 (m, 1H), 4.03-4.14 (m, 3H), 4.27 (dd, *J* = 2.3, 8.4 Hz, 1H), 4.38 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.68-4.80 (m, 4H), 4.85 (dd, *J* = 2.3, 5.8 Hz, 1H), 4.92 (d, *J* = 11.5 Hz, 1H), 7.23-7.40 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 24.0, 29.27, 29.34, 29.46, 29.55, 29.63, 29.67, 31.4, 31.9, 53.5, 67.3, 68.9, 69.0, 72.75, 72.80, 73.3, 73.6, 74.3, 74.7, 75.4, 79.7, 80.1, 80.8, 86.0, 91.6, 127.5, 127.63, 127.69, 127.87, 127.96, 128.1, 128.2, 128.33, 128.39, 128.40, 128.43, 128.9, 137.6, 137.9, 138.3, 138.4, 153.8; (ESI-HRMS $[M+H]^+$ calcd for *m/z* $C_{55}H_{69}Cl_3NO_7^+$ 960.4134, found 960.4130.

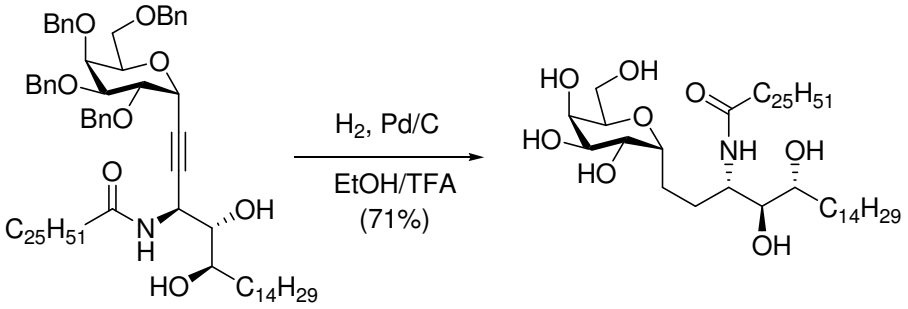


Compound 24. To a solution of **21** (333 mg, 0.346 mmol) in THF (15 mL) was added 1 M HCl (5 mL). After being stirred at rt for 30 min, the reaction mixture was carefully basified with saturated aqueous $NaHCO_3$ solution (5 mL). The product was extracted with CH_2Cl_2 (3×50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated to obtain crude product **22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.1 Hz, 3H), 1.17-1.46 (m, 24H), 1.50-1.59 (m, 1H), 1.62-1.71 (m, 1H), 2.66 (d, *J* = 9.2 Hz, 1H), 3.06 (d, *J* = 9.1 Hz, 1H), 3.43 (dd, *J* = 6.9, 9.3 Hz, 1H), 3.49 (dd, *J* = 5.9, 9.3 Hz, 1H), 3.54-3.59 (m, 1H), 3.61-3.68 (m, 1H), 3.80 (dd, *J* = 2.7, 9.8 Hz, 1H), 3.91-3.93 (m, 1H), 3.97-4.01 (m, 1H), 4.10 (dd, *J* = 6.0, 9.8 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.44 (d, *J* = 11.7 Hz, 1H), 4.56 (d, *J* = 11.4 Hz, 1H), 4.68 (d, *J* = 11.7 Hz, 1H), 4.74-4.84 (m, 4H), 4.89 (dt, *J* = 2.7, 8.5

Hz, 1H), 4.92 (d, J = 11.6 Hz, 1H), 7.23-7.44 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.7, 29.4, 29.51, 29.56, 29.61, 29.64, 29.68, 31.9, 33.3, 45.2, 67.3, 68.6, 72.2, 72.8, 72.9, 73.5, 73.7, 73.9, 74.3, 74.8, 75.5, 80.0, 81.3, 83.0, 92.1, 127.6, 127.7, 127.86, 127.97, 128.07, 128.16, 128.26, 128.31, 128.43, 128.47, 128.54, 137.4, 137.5, 138.2, 138.3, 161.0; ESI-HRMS $[M+NH_4]^+$ calcd for m/z $C_{55}H_{74}Cl_3N_2O_8^+$ 995.4505, found 995.4503.

To crude **22** in EtOH (10 mL) was added aqueous 6 *N* NaOH (5 mL). The air was replaced with nitrogen, and the solution was stirred at rt for 6 h. Et_2O (50 mL.) was added, the organic layer was separated, the aqueous layer was washed with Et_2O (2×50 mL), dried (K_2CO_3), and filtered. Concentration afforded **23** as a white solid residue (195 mg, 68% two steps from **21**). To a solution of the crude amine **23** in THF (5 mL) were added Et_3N (163 μL, 1.17 mmol) and hexacosanoyl chloride[3, 28] (0.281 mmol, in 1 mL of THF) at 0 °C. The mixture was stirred at rt for 30 min, quenched with saturated aqueous NH_4Cl solution, and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by flash chromatography (EtOAc/hexanes 1:3 to 1:2) to yield amide **24** (208 mg, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.1 Hz, 6H), 1.15-1.42 (m, 70H), 1.50-1.65 (m, 2H), 2.15 (t, J = 7.1 Hz, 2H), 2.65 (br s, 1H), 3.16 (br s, 1H), 3.42-3.53 (m, 1H), 3.55-3.63 (m, 1H), 3.78-3.83 (m, 1H), 3.90-3.93 (m, 1H), 3.98 (t, J = 5.8 Hz, 1H), 4.08 (dd, J = 5.8, 9.6 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.45 (d, J = 11.7 Hz, 1H), 4.56 (d, J = 11.4 Hz, 1H), 4.68 (d, J = 11.7 Hz, 1H), 4.74-4.86 (m, 4H), 4.93 (d, J = 11.4 Hz, 1H), 5.00 (d, J = 7.7 Hz, 1H), 6.08 (d, J = 8.0 Hz, 1H), 7.22-7.46 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.1, 22.7, 25.5, 25.9, 29.25,

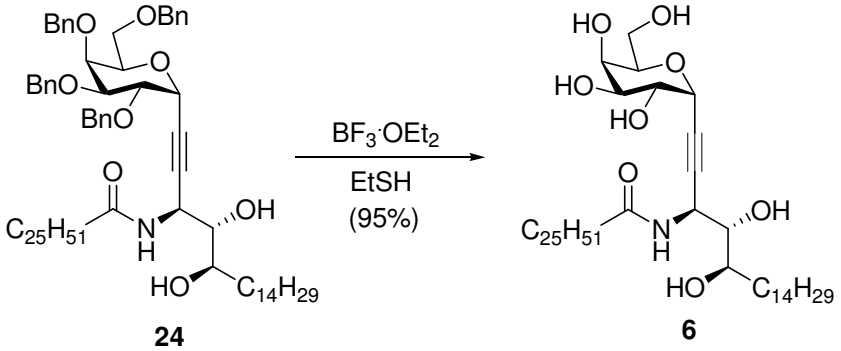
29.32, 29.34, 29.48, 29.53, 29.59, 29.63, 29.68, 31.9, 33.5, 36.5, 42.9, 67.3, 68.6, 72.5, 72.7, 72.9, 73.5, 73.7, 74.4, 74.7, 74.8, 75.5, 79.79, 79.83, 85.0, 127.62, 127.95, 127.8, 127.96, 128.02, 128.08, 128.2, 128.4, 128.5, 137.4, 137.6, 138.3, 138.5, 146.1, 172.3; ESI-HRMS $[M+H]^+$ calcd for *m/z* $C_{79}H_{122}NO_8^+$ 1212.9165, found 1212.9184.



24 **2**

***N*-((3*S*,4*S*,5*R*)-1-(α-*C*-D-Galactopyranosyl)-nonadecane-4,5-diol-3-yl)-hexacosanamide (2).** Amide **24** (48 mg, 0.040 mmol) was suspended in EtOH (95%)/TFA (30:1, 10.3 mL) at rt. After Pd/C (100 mg, 10% Pd) was added, the reaction vessel was purged with H_2 for 10 min. The mixture was stirred at rt for 48 h under a balloon filled with H_2. The suspension was filtered through Celite, which was washed with $CHCl_3$/MeOH (1:1, 30 mL) followed by pyridine (20 mL). The filtrate was concentrated, and the residue was purified by flash chromatography ($CHCl_3$/MeOH 8:1) and was then lyophilized with benzene to afford **2** (24 mg, 71%) as a white powder: $[\alpha]^{25}_D$ +33.7 (*c* 0.2, pyridine) [lit.[2a] $[\alpha]^{25}_D$ +38.4 (*c* 0.13, pyridine); lit.[3] $[\alpha]^{25}_D$ +40.8 (*c* 0.13, pyridine)]; ^{1}H NMR (500 MHz, d_5-pyridine) δ 0.87 (t, *J* = 6.4 Hz, 6H), 1.16-1.50 (m, 66H), 1.66-1.76 (m, 1H), 1.82-1.91 (m,

2H), 1.90-2.01 (m, 2H), 2.17-2.27 (m, 1H), 2.28-2.40 (m, 2H), 2.43-2.52 (m, 2H), 2.57-2.67 (m, 1H), 2.71-2.80 (m, 1H), 4.19-4.29 (m, 4H), 4.38 (dd, *J* = 4.6, 11.2 Hz, 1H), 4.50-4.57 (m, 3H), 4.76 (dd, *J* = 5.5, 8.9 Hz, 1H), 5.14-5.21 (m, 1H), 8.55 (d, *J* = 9.0 Hz, 1H); ^{13}C NMR (125 MHz, d_5-pyridine) δ 14.8, 23.4, 26.9, 30.1, 30.1, 30.3, 30.5, 30.7, 32.6, 34.9, 37.4, 53.1, 63.2, 70.8, 71.1, 72.7, 73.0, 74.2, 77.6, 79.0, 173.8; ESI-HRMS $[M+H]^+$ calcd for *m/z* $C_{51}H_{101}NNaO_8^+$ 878.7419, found 878.7420. Table 1.1 shows that the ^{1}H and ^{13}C NMR spectra and the $[\alpha]^{25}_D$.value are in full agreement with the literature data.[2a, 3, 29]



24 **6**

***N*-((3*S*,4*S*,5*R*)-1-(α-*C*-D-Galactopyranosyl)-nonadec-1-ynyl-4,5-diol-3-yl)-hexacosanamide (6).** A solution of **24** (9.5 mg, 7.83 μmol) in EtSH/BF_3·OEt_2 (3:1, 1.3 mL) was stirred at rt for 24 h. The solvent was evaporated, and the residue was purified by column chromatography ($CHCl_3$/MeOH 10:1) and lyophilized with benzene to afford **6** (6.3 mg, 95%) as a white powder: $[\alpha]^{25}_D$ +62.2 (*c* 0.09, pyridine); ^{1}H NMR (400 MHz, d_5-pyridine) δ 0.85-0.90 (m, 6H), 1.16-1.52 (m, 66H), 1.65-1.84 (m, 3H), 1.86-1.98 (m, 2H), 2.29-2.38 (m, 1H), 2.41 (t, *J* = 7.5 Hz, 2H),

Table 4.1 Comparison of ^{1}H and ^{13}C NMR and specific rotation data.

	Ref. 29	Ref. 3	Our data
^{1}H (500 MHz, d_5-pyridine)	8.47 (d, *J* = 8.8 Hz, 1H) 5.14 (m, 1H) 4.74 (dd, *J* = 5.8, 8.8 Hz, 1H) 4.52 (m, 3H) 4.37 (dd, *J* = 4.3, 11.0 Hz, 1H) 4.25 (m, 4H) 2.72 (m, 1H) 2.59 (m, 1H) 2.48 (m, 1H) 2.33 (m, 2H) 2.22 (m, 1H) 1.94 (m, 2H) 1.86 (m, 3H) 1.71 (m, 1H) 1.37 (m, 64H) 0.88 (t, *J* = 6.4 Hz, 6H)	8.37 (d, *J* = 8.9 Hz, 1H) 5.09 (dd, 1H) 4.70 (dd, *J* = 5.5, 8.7 Hz, 1H) 4.55-4.43 (m, 3H) 4.35 (dd, *J* = 4.5, 11.2 Hz, 1H) 4.26-4.15 (m, 4H) 2.75-2.62 (m, 1H) 2.61-2.51 (m, 1H) 2.51-2.37 (m, 2H) 2.37-2.25 (m, 2H) 2.25-2.13 (m, 1H) 2.00-1.78 (m, 4H) 1.78-1.61 (m, 1H) 1.50-1.21 (m, 68H) 0.89 (t, *J* = 6.4 Hz, 6H)	8.55 (d, J = 9.0 Hz, 1H) 5.21-5.14 (m, 1H) 4.76 (dd, *J* = 5.5, 8.9 Hz, 1H) 4.57-4.50 (m, 3H) 4.38 (dd, *J* = 4.6, 11.2 Hz, 1H) 4.29-4.19 (m, 4H) 2.80-2.71 (m, 1H) 2.67-2.57 (m, 1H) 2.52-2.43 (m, 2H) 2.40-2.28 (m, 2H) 2.27-2.17 (m, 1H) 2.01-1.90 (m, 2H) 1.91-1.82 (m, 2H) 1.76-1.66 (m, 1H) 1.50-1.16 (m, 66H) 0.87 (t, *J* = 6.4 Hz, 6H)
^{13}C (125 MHz, d_5-pyridine)	173.8, 78.8, 77.3, 74.0, 73.0, 72.5, 70.9, 70.7, 63.1, 53.0, 37.3, 34.8, 32.4, 30.7, 30.5, 30.3, 30.1, 29.9, 26.9, 23.3, 14.6	173.8, 78.8, 77.3, 74.1, 73.0, 72.5, 70.9, 70.8, 63.1, 53.1, 37.3, 34.8, 32.4, 30.7, 30.5, 30.3, 30.1, 29.9, 26.9, 23.0, 14.6	173.8, 79.0, 77.6, 74.2, 73.0, 72.7, 71.1, 70.8, 63.2, 53.1, 37.4, 34.9, 32.6, 30.7, 30.5, 30.3, 30.1, 30.1, 26.9, 23.4, 14.8
$[\alpha]^{25}_{D}$	+40.8 (*c* 0.13 pyridine)	+38.4 (*c* 0.13 pyridine)	+33.7 (*c* 0.20 pyridine)

4.26 (dd, J = 3.1, 8.3 Hz, 1H), 4.33-4.43 (m, 2H), 4.47-4.57 (m, 3H), 4.70-4.79 (m, 2H), 5.30 (dd, J = 1.6, 5.9 Hz, 1H), 6.36 (dt, J = 2.2, 8.8 Hz, 1H), 9.23 (d, J = 8.8 Hz, 1H); ^{13}C NMR (100 MHz, d_5-pyridine) δ 14.7, 23.4, 26.7, 30.1, 30.22, 30.26, 30.30, 30.39, 30.46, 30.50, 30.6, 30.9, 32.6, 35.3, 37.1, 46.1, 63.0, 69.8, 71.0, 71.2, 73.1, 73.4, 76.2, 78.5, 81.5, 87.6, 172.8; ESI-HRMS $[M+H]^+$ calcd for m/z $C_{51}H_{98}NO_8^+$ 852.7287, found 852.7287.

4.6 References and Notes

(1) The Tetramer Core Facility funded by NIH provides reagents for NKT cell activation, including CD1d ligands, to approved investigators.

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(9) Synthesis of primary alcohol **18** was readily achieved by following a reported synthesis of a shorter chain analog from 1-heptene. Smith, A. B.; Chen, S. S. Y.; Nelson, F. C.; Reichert, J. M.; Salvatore, B. A. *J. Am. Chem. Soc.* **1997**, *119,* 10935.

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(11) **15** was reduced back to **18** by $NaBH_4$ and subsequently converted to the (*S*)-MTPA ester using (*R*)-MTPA chloride. The ^1H NMR spectrum of the MTPA ester exhibited no signals of the other isomer.

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(16) **7** was converted to the (*S*)-MTPA ester using using (*R*)-MTPA chloride. The de value was determined by analyzing the ^1H NMR spectrum of the (*S*)-MTPA ester of **7**.

(17) Two mechanisms may be responsible for the failure: (1) Intramolecular 1,3-dipolar cycloaddition of the propargyl azide followed by MeOH attack on the resulting strained bicyclic triazole or (2) a triaza-Cope rearrangement followed by cyclization of the resulting allenyl azide to triazafulvene and reaction with MeOH. See: (a) Banert, K. *Chem. Ber.* **1989**, *122*, 911. (b) Banert, K. *Chem. Ber.* **1989**, *122*, 1963.

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S.; Liu, J.; Tigyi, G.; Bittman, R. *J. Org. Chem.* **2009**, *74*, 3192. (d) The preparation of **8** in the presence of a catalytic amount of DBU[18b] was ineffective.

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(20) The spectral data of **2** matched well with the previously reported material in 500-MHz ^{1}H and 125-MHz ^{13}C NMR spectra and optical rotation (see Table 1.1).[2, 3]

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(23) Peracetylation of D-galactose (**A**) using Ac_2O as the solvent proceeded in low yield (30% to 55%), [22a, b] because of the formation of an α- and β-mixture of D-galactopyranose pentaacetate and D-galactofuranose pentaacetate.[22c] Although the reaction in pyridine worked well,[22d, e] pyridine is high boiling, noxious and also not well suited for use in large scale preparation.[22f]

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are: (*S*,*S*)-**12**: $[\alpha]^{25}_{D}$ +38.7 (*c* 0.63, $CHCl_3$), [lit.[25] $[\alpha]^{25}_{D}$ +49.8 (*c* 3.0, $CHCl_3$), Sigma-Aldrich: $[\alpha]^{25}_{D}$ +50 (*c* 1.0, $CHCl_3$)]; (*R*,*R*)-**12**: $[\alpha]^{25}_{D}$ -40.9 (*c* 0.65, $CHCl_3$), [Sigma-Aldrich: $[\alpha]^{25}_{D}$ -50 (*c* 1.0, $CHCl_3$)].

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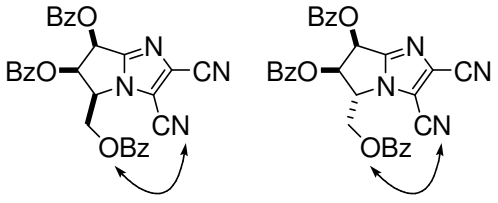

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Chapter 4

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(16) **7** was converted to the (*S*)-MTPA ester using using (*R*)-MTPA chloride. The de value was determined by analyzing the ^1H NMR spectrum of the (*S*)-MTPA ester of **7**.

(17) Two mechanisms may be responsible for the failure: (1) Intramolecular 1,3-dipolar cycloaddition of the propargyl azide followed by MeOH attack on the resulting strained bicyclic triazole or (2) a triaza-Cope rearrangement followed by cyclization of the resulting allenyl azide to triazafulvene and reaction with MeOH. See: (a) Banert, K. *Chem. Ber.* **1989**, *122*, 911. (b) Banert, K. *Chem. Ber.* **1989**, *122*, 1963.

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