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Stereoselective synthesis of β-amino alcohols and glycosphingolipids: N-diphenylmethylene protection for tandem C-C/C-O bond formation

Peterson, Matt Anders, Ph.D.
The University of Arizona, 1992
STEREOSELECTIVE SYNTHESIS OF β-AMINO ALCOHOLS AND GLYCOSPHINGOLIPIDS:
N-DIPHENYLMETHYLENE PROTECTION FOR TANDEM C-C/O BOND FORMATION

by

Matt Anders Peterson

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A Dissertation Submitted to the Faculty of the
DEPARTMENT OF CHEMISTRY
In Partial Fulfillment of the Requirements
For the Degree of
DOCTOR OF PHILOSOPHY
In the Graduate College
THE UNIVERSITY OF ARIZONA

1992
As members of the Final Examination Committee, we certify that we have read the dissertation prepared by Matt Anders Peterson entitled Stereoselective Synthesis of β-Amino Alcohols and Glycosphingolipids: N-Diphenylmethylene Protection for Tandem C-C/C-O Bond Formation and recommend that it be accepted as fulfilling the dissertation requirement for the Degree of Doctor of Philosophy.

Dr. Robin L. Polt
Date 11/10/92

Dr. Robert B. Bates
Date 11/10/92

Dr. Eugene A. Mash
Date 11/10/92

Dr. William A. Remers

Dr. David G. Wigley

Final approval and acceptance of this dissertation is contingent upon the candidate's submission of the final copy of the dissertation to the Graduate College.

I hereby certify that I have read this dissertation prepared under my direction and recommend that it be accepted as fulfilling the dissertation requirement.

Dissertation Director Dr. Robin L. Polt
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SIGNED: [Signature]

Matt A. Peterson
ACKNOWLEDGEMENTS

I would like to extend my sincere thanks to my research advisor Dr. Robin L. Polt for the many helpful discussions held during the course of this research. Without his invaluable insight and advice, the solutions to the synthetic problems discussed in this dissertation would not have been possible.

A sincere debt of gratitude is also owed my co-workers Thusitha Wijayaratne and Dr. Lajos Szabo. Many useful discussions concerning my chemistry were held over the years. Their critiques, advice, and different points of view are greatly appreciated. For their friendship I thank them most. Their unwavering support and encouragement helped me overcome the many obstacles and pitfalls that were encountered along the way.
DEDICATION

This dissertation is dedicated to my wife and children for their patient endurance of many lonely nights and weekends without the company of a husband or a father.
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ABSTRACT

A new method for *threo*-selective synthesis of β-amino alcohols is described. This method employs N-diphenylmethylene-protected α-amino esters as starting materials. The α-amino ester is reduced to the oxidation state of an aldehyde with DIBAL or DIBAL:TRIBAL (1:1) followed by sequential addition of various Grignards and alkenyllithiums. The method is highly *threo*-selective (stereoselectivities ranged from 8:1 to > 20:1) and provides norpseudoephedrine and *threo*-sphingosine analogs in enantiomerically enriched form (> 97% ee).

The mechanism of C-C bond formation was examined. A stable aluminoxy-acetal intermediate (generated by DIBAL reduction of the ester) was trapped with TMS-imidazole and isolated as the corresponding siloxy-acetal. The stereochemical outcome of the C-C bond forming step was shown to correlate with the steric bulk of the ester moiety. Bulky ester groups showed the greatest degree of *threo*-selectivity. These results suggest that the aluminoxy-acetal intermediate may be involved in determining stereoselectivity via either a tight-ion $S_N^1$-like or $S_N^2$-like reaction mechanism.

A series of glycosyl acceptors was synthesized from N-diphenylmethylene-protected *threo*-sphingosine derivatives. These glycosyl acceptors undergo β-specific glycosylation using the method developed in this laboratory. This method capitalizes on a favorable hydrogen-bonding pattern imparted by the N-diphenylmethylene-protection. The favorable hydrogen-bonding enhances the nucleophilicity of the glycosyl acceptor relative to glycosyl acceptors with more conventional N-protection (*i.e.* Cbz, Boc, acyl *etc*.). This enhanced nucleophilicity allows the glycosylation to be carried out under mild conditions (AgOTf, CH$_2$Cl$_2$, RT overnight) and provides the corresponding β-glycosphingolipids in approximately 70% chemical yield.
CHAPTER 1

N-DIPHENYL METHYLENE-PROTECTED α-AMINO ESTERS AS PRECURSORS FOR β-AMINO ALCOHOLS: C-C BOND FORMATION VIA CHELATION CONTROL
1.1 Introduction

Optically active β-amino alcohols are important naturally occurring compounds which possess a wide range of biological activity. Some representative examples (Scheme 1.1) include (1) pretazettine, an anti-tumor compound which exhibits activity against Rauscher leukemia, Lewis lung carcinoma and AKR leukemia,¹ (2) sphingosine, a potent protein kinase C inhibitor,² (3) statine, the β-hydroxy-γ-amino acid constituent responsible for the protease inhibitory action of pepstatin³ and (4) dendrobine, an Orchidaceae alkaloid exhibiting anti-pyretic and hypotensive activity.⁴

\[
\text{Statine}
\]

\[
\text{Pretazettine}
\]

\[
\text{Dendrobine}
\]

\[
\text{Sphingosine}
\]

Scheme 1.1
In addition to naturally occurring compounds, synthetic β-amino alcohols are known to possess potent pharmacological properties as well.\textsuperscript{5}

Due to the wide range of biological activities exhibited by β-amino alcohols, their stereoselective synthesis remains an area of intense interest for the synthetic organic chemist. Many ingenious and highly effective stereoselective methods have been developed. These methods may be grouped into five general categories: (1) 1,2-addition of organometallic reagents or hydrides to carbonyl or imine species bearing a chiral center at the α position,\textsuperscript{6} (2) functionalization of alkenes either in the presence of a chiral auxiliary or chiral catalyst,\textsuperscript{7} (3) 1,4-addition to nitroolefins,\textsuperscript{8} (4) nucleophilic inversion of a pre-existing chiral center\textsuperscript{9} and (5) intramolecular heterocyclizations of chiral hetero-atom bearing alkenes or allenes followed by ring cleavage (Scheme 1.2).\textsuperscript{10}

Of these approaches the first has received the greatest attention. This is largely because the chiral precursors for most of these 1,2-additions are readily available α-amino or α-hydroxy acids. The ready availability of α-amino and α-hydroxy acids, coupled with their inexpensive price and the stereocontrol their existing chiral center may impart, make them attractive starting materials for the synthesis of β-amino alcohols. For example, α-amino acids have been the starting material of choice in many of the statine and hydroxyethylene dipeptide isostere syntheses developed to date.\textsuperscript{11,6f,i,h,t} Stereoselective syntheses of sphingosine have also depended heavily on the α-amino acid serine as a chiral precursor.\textsuperscript{12}
Type 1 - 1,2-Addition to Carbonyls

Scheme 1.2
Type 2 - Functionalization of Alkenes

(Kunieda et al.)

Type 3 - 1,4-Addition to Nitroolefins

(Kamimura and Ono)

Type 4 - Nucleophilic Inversion of a Pre-existing Chiral Center

(Sharpless et al.)

Type 5 - Intramolecular Heterocyclization of Chiral Hetero-atom Bearing Alkenes or Allenes

(Scheme 1.2 (Continued))

(Tamao et al.)
The use of α-amino acids in β-amino alcohol syntheses usually follows one of two strategies: (1) reduce the acid or acid derivative (e.g. ester) to the corresponding α-amino aldehyde, then react this with an appropriate organometallic reagent \(^{6a-h}\) or (2) add an appropriate organometallic reagent to the acid or acid derivative (N-methoxymethylamide), then reduce the resulting α-amino ketone with an appropriate reagent such as NaBH\(_4\), Zn(BH\(_4\))\(_2\) or LiBH\(_4\).\(^{6i-k}\) These methods have met with considerable success (depending on the conditions), but suffer from the α-amino center being configurationally labile and therefore easily racemized. α-Amino aldehydes are particularly prone to racemization.\(^{13}\) Because of this configurational lability, α-amino aldehydes must be used in situ (without isolation), or used immediately after isolation via flash chromatography. Conventional gravity driven chromatography has been shown to cause significant racemization.\(^{13b}\) This racemization problem seems to be partially dependent on the amino protecting group used. For example, racemization has been observed in both Cbz- and Boc-protected α-amino aldehydes.\(^{13b,6f}\) Evidence also indicates that Boc-protected α-amino aldehydes racemize under the conditions necessary for C-C bond formation.\(^{13d,e}\) Recently two new protecting groups have been developed which avoid this problem (Scheme 1.3).\(^{14}\)
Garner's method$^{14a}$ is useful for β-hydroxy amino aldehydes such as threonine and serine which form the 3° Boc-protected amine, but is not applicable to other α-amino aldehydes. Rapoport's method$^{14b}$ is more general but requires more than one step for protection and is tedious.
1.2 N-Diphenylimethylene-Protected α-Amino Esters as Precursors for β-Amino Alcohols

Because of the current interest in β-amino alcohols and the problems associated with one of the most popular synthetic methods (i.e. racemization of N-protected α-amino aldehyde precursors), a new method for stereoselective β-amino alcohol syntheses was sought. A recent report by S. D. Burke et al.\textsuperscript{15} (Scheme 1.4) wherein chiral α-alkoxy esters are converted to either threo (syn) or erythro (anti) 1,2-diols in one step suggested that a similar protocol involving α-amino esters might be developed for the synthesis of β-amino alcohols. It was hoped that this new method would capitalize on the ready availability of α-amino acids, provide a high degree of stereocontrol and access to a variety of β-amino alcohols, while at the same time avoid the problem of racemization.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {OH};
\node (b) at (-1,0) {OH};
\node (c) at (0,-1) {OR};
\node (d) at (-1,-1) {OR};
\node (e) at (2,0) {OH};
\node (f) at (3,0) {OH};
\node (g) at (2,-1) {OR};
\node (h) at (3,-1) {OR};
\draw (a) -- (b); \draw (c) -- (d); \draw (e) -- (f); \draw (g) -- (h);
\node at (0,-2) {Erythro (Anti)};
\node at (-1,-2) {51-93\%};
\node at (-1,-2.5) {6:1 to 20:1};
\node at (2,-2) {Threo (Syn)};
\node at (3,-2) {72-87\%};
\node at (3,-2.5) {6:1 to 15:1};
\node at (3,-2.5) {S. D. Burke et al.\textsuperscript{15}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.4}

Assuming that a suitable amino protecting group could be found, it seemed likely that a low temperature one-pot method similar to the one developed by Burke\textsuperscript{15} would provide the stereocontrol and configurational stability necessary for an efficient
stereoselective synthesis of $\beta$-amino alcohols from $\alpha$-amino esters. The diphenylmethylene protecting group developed by O'Donnell\textsuperscript{16} (Scheme 1.5) was examined for this purpose.

Scheme 1.5

N-Diphenylmethylene-protected $\alpha$-amino esters are easily prepared highly stable crystalline compounds. They may be stored for months at room temperature in a dessicator with no sign of decomposition.\textsuperscript{17} Although pKa's for the $\alpha$-protons are low (glycine = 18.7, alanine = 22.8, phenylalanine = 23.2),\textsuperscript{18} studies performed by O'Donnell and Polt indicate that N-diphenylmethylene-protected $\alpha$-amino esters are configurationally stable under both acidic and mildly basic conditions.\textsuperscript{17a} This configurational stability, coupled with the availability of a lone pair of electrons on nitrogen suggested that O'Donnell's protecting group would provide the qualities desired:

(1) ready availability of chiral precursor
(2) ease of synthesis
(3) stability (both configurational and overall)
(4) high degree of stereoselectivity

The first two points seemed relatively well addressed: the ease of synthesis and availability were already well known. Overall stability has been demonstrated. But
what about stereoselectivity? Would the Schiff base esters provide the necessary stereocontrol?

It was reasoned that the lone pair electrons on nitrogen and a lone pair on the ester carbonyl would form a tight chelate with a metal and that subsequent nucleophilic attack would occur from the sterically less congested side in agreement with the Cram-chelate model for carbonyl addition (Scheme 1.6).¹⁹

![Cram-Chelate Model](image)

Scheme 1.6

Several reports have implicated the chelating ability of the lone pair electrons on imine nitrogens. This chelation has been invoked as markedly influencing the stereochemical outcome of the reaction.²⁰ Based on these reports it seemed likely that the Schiff base esters would indeed provide the chelation required and that threo and erythro β-amino alcohols could be obtained with a fair degree of stereocontrol (Scheme 1.7).
An additional question to be addressed concerned the reactivity of the imine toward nucleophilic reagents. Studies by O'Donnell showed the Schiff base to be stable to attack by nucleophiles such as alcohols or amines, higher order mixed organocuprates, organoboranes and sodium dimethylmalonate. In doubt remained the reactivity of the diphenylmethylene protecting group towards organometallic reagents such as Grignards or alkyl or alkenyllithiums and reducing agents such as NaBH₄, Zn(BH₄)₂, LiBH₄ and DIBAL.
1.3 Preliminary Studies—Establishing the Reactivity of the N-Diphenylmethylene Protecting Group Toward Organometallic Reagents and Metal Hydrides

In order to establish the suitability of the N-diphenylmethylene protecting group for the proposed β-amino alcohol synthesis, it was necessary to determine its stability toward the organometallic reagents and common metal hydrides that would be used in the process. For this purpose a series of Schiff base esters was synthesized (Table 1).\textsuperscript{17a}

\[
\text{\begin{align*}
R & \quad \text{Diphenylketimine,} \\
\text{HCl \cdot H_2N} & \quad \text{CH}_2\text{Cl}_2, \text{RT}, 24 \text{~h} \\
\text{R' \quad OR'} & \quad \text{Ph} = \text{N} \quad \text{Ph}
\end{align*}}
\]

Table 1

<table>
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<tr>
<th>Compound</th>
<th>R</th>
<th>R'</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>CH\textsubscript{3}</td>
<td>Et</td>
<td>80%</td>
</tr>
<tr>
<td>1b</td>
<td>PhCH\textsubscript{2}</td>
<td>CH\textsubscript{3}</td>
<td>76%</td>
</tr>
<tr>
<td>1c</td>
<td>HOCH\textsubscript{2}</td>
<td>CH\textsubscript{3}</td>
<td>89%</td>
</tr>
<tr>
<td>1d</td>
<td>TBDMSOCH\textsubscript{2}O</td>
<td>CH\textsubscript{3}</td>
<td>92%</td>
</tr>
<tr>
<td>1e</td>
<td>H</td>
<td>Et</td>
<td>ref. 17</td>
</tr>
</tbody>
</table>

All of the Schiff base esters thus prepared were crystalline and stable for months when stored at room temperature in a dessicator.\textsuperscript{22}
The reactivity of the benzophenone Schiff base was demonstrated by the following reactions (Scheme 1.8).

Upon treatment of 1a with excess PhMgBr at -78 °C followed by warming to room temperature for 45 min, no addition of Grignard to the imine was observed. Treatment of 1b with 2.5 eq DIBAL and 3 eq PhMgBr at -78 °C in CH₂Cl₂ for 10 h provided 2b in 91% yield. Reaction of 1a with 7 eq DIBAL resulted in complete reduction of both
the ester and the imine. When 1b was treated with 4 eq PhMgBr at -78 °C, warmed to room temperature for 2 hours, then rechilled to -78 °C and treated with 7 eq DIBAL, compound 2d was obtained in 73% yield.

Clearly, the Schiff base protecting group was inert toward PhMgBr addition at both -78 °C and room temperature. Excess DIBAL reduced the imine to the benzhydryl amine. When only two equivalents of DIBAL were added, no reduction of the imine was observed. Clearly the Schiff base was less reactive than the ester with respect to DIBAL reduction. The latter result bode well for the proposed threo (syn) selective β-amino alcohol synthesis (Scheme 1.7) where DIBAL is typically used as reducing agent. However, the former result (i.e. complete reduction of the imine in the presence of excess DIBAL) did not bode well for the synthesis of the erythro (anti) isomer via the procedure outlined in Scheme 1.7 (excess LiBH₄ in THF was used as reducing agent by both Comins²³ and Burke¹⁵ (Scheme 1.4) in similar reactions).

As might have been predicted based on the reactivity of the imine toward DIBAL, when Schiff base ester 1a was treated with LiBH₄ and PhMgBr at -20 °C in an attempt to synthesize the erythro β-amino alcohol norephedrine (using conditions similar to those established by Comins²³ and Burke¹⁵), reduction of the imine occurred and no desired product was detected. This result suggested that the Comins/Burke conditions for erythro-selectivity were inappropriate for N-diphenylmethylene-protected α-amino esters. Attention was therefore turned to the more promising threo (syn) approach.
1.4 Stereoselective Synthesis of Norpseudoephedrines

Norpseudoephedrine is a naturally occurring alkaloid isolated from the leaves of the kat plant, *Catha edulis* Forsk., *Celastraceae*, an evergreen shrub native to Southern Arabia and Ethiopia. It is also present in the mother liquor from the chinese drug Ma Huang after the recovery of ephedrine.²⁴ Though structurally related to ephedrine, norephedrine and pseudoephedrine (Scheme 1.9), norpseudoephedrine differs significantly in its pharmacological properties.²⁵ Like norephedrine however, norpseudoephedrine is an appetite supressant and is widely used around the world as an anorexic agent.²⁶

Due to the simplicity of its structure and the fact that all of its stereoisomers are well-characterized, norpseudoephedrine was chosen as an initial target for development of a *threo*-selective methodology based on N-diphenylmethylene-protected α-amino esters.
The first attempts at synthesizing norpseudoephedrine involved treatment of the Schiff base esters with one equivalent of DIBAL and PhMgBr. These conditions proved to be unsuccessful. When Schiff base ester 1a was treated sequentially with one equivalent of DIBAL and 3 equivalents of PhMgBr in CH$_2$Cl$_2$ at -78 °C, a mixture consisting of approximately 50% completely reduced ester and 50% product resulting from addition of two PhMgBr to the ester was obtained. When the Schiff base was treated with only one equivalent of DIBAL, a mixture consisting of 50% completely reduced ester to 50% starting material was obtained. These results seemed to implicate a 2:1 complex between the aluminum hydride and the Schiff base ester (Scheme 1.10).

Scheme 1.10
The exact structure of this complex is presently unknown, but a 2:1 complex is consistent with similar examples found in the literature (Scheme 1.11).\textsuperscript{27}

Scheme 1.11
In addition to this literature precedent, complex formation of some sort is indicated by
the bright yellow color which forms upon addition of even a few drops of DIBAL to a solution of Schiff base ester at -78 °C.²⁸

In order to satisfy this apparent 2:1 stoichiometry, two equivalents of DIBAL were added to the Schiff base ester at -78 °C. Three equivalents of PhMgBr were then added, followed by warming to room temperature. When this procedure was followed, N-diphenylmethylened-protected norspeudoephedrine and norpseudoephedrine analogs were obtained in 54-69% chemical yield and approximately 8:1 syn : anti selectivity (Table 2).

![Chemical structure and reaction](image)

Table 2

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield</th>
<th>Syn : Anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>CH₃</td>
<td>54%</td>
<td>8.8 : 1</td>
</tr>
<tr>
<td>3b</td>
<td>PhCH₂</td>
<td>69%</td>
<td>8.0 : 1</td>
</tr>
<tr>
<td>3c</td>
<td>HOCH₂</td>
<td>-</td>
<td>----</td>
</tr>
<tr>
<td>3d</td>
<td>TBDMSOCH₂</td>
<td>62%</td>
<td>8.0 : 1</td>
</tr>
<tr>
<td>3e</td>
<td>H</td>
<td>64%</td>
<td>----</td>
</tr>
</tbody>
</table>
When THF was used as reaction solvent, no addition product was observed. The only product was the completely reduced 1° imino alcohol. When CH₂Cl₂ was used as solvent, addition products were obtained with the yields shown in Table 2. The PhMgBr used in the reactions depicted in Table 2 was commercially prepared by Aldrich as a 3.0 M solution in Et₂O. When PhMgBr generated in THF was used, stereoselectivities dropped drastically to 3:1 (syn: anti). The major by-products of these reactions (using either PhMgBr (Et₂O) or PhMgBr (THF)) were the completely reduced 1° imino alcohols (Scheme 1.12).

Scheme 1.12

Since two equivalents of DIBAL were required in order to satisfy the 2:1 hydride : substrate complex, an "extra" equivalent of hydride was available to compete with the Grignard for nucleophilic attack of the ester. It was reasoned that the major by-product (1° imino alcohol) arose due to the successful competition of this extra hydride. It seemed probable that this undesired reduction could be avoided (and higher chemical yields obtained) if the offending second equivalent of DIBAL could be replaced by some non-hydrido alkylaluminum. To this end, the reactions shown in Table 2 were
repeated using one equivalent of 1:1 mixtures of DIBAL and various alkylaluminums (Scheme 1.13).

\[
1:1 \text{ Alkylaluminum : DIBAL Mixtures} \\
\text{Trisobutylaluminum : DIBAL} \\
\text{Diethylaluminum chloride : DIBAL} \\
\text{Trimethylaluminum : DIBAL} \\
\text{Diisobutylaluminum phenoxide : DIBAL}
\]

![Scheme 1.13](image-url)
As expected, several replacements for the extra equivalent of hydride (X = Cl, OPh, iBu) were found to be effective. TLC experiments indicated that the DIBAL:diethylaluminum chloride, DIBAL:diisobutylaluminum phenoxide, and DIBAL:triisobutylaluminum were equally successful in avoiding the competing reduction. DIBAL:trimethylaluminum (1:1) was unsuccessful due to competing addition of the methyl groups. For practical reasons (i.e. ease of preparation, stability etc.) the DIBAL:TRIBAL (1:1) mixture in hexanes (D:T) was used to repeat the chemistry shown in Table 2 (Table 3).

Table 3

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield (D:T)</th>
<th>Yield (2 Dibal)</th>
<th>Syn : Anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>CH₃</td>
<td>78%</td>
<td>54%</td>
<td>8.8 : 1</td>
</tr>
<tr>
<td>3b</td>
<td>PhCH₂</td>
<td>75%</td>
<td>69%</td>
<td>8.0 : 1</td>
</tr>
<tr>
<td>3c</td>
<td>HOCH₂</td>
<td>- - - -</td>
<td>- - - -</td>
<td>- - -</td>
</tr>
<tr>
<td>3d</td>
<td>TBDMSOCH₂</td>
<td>73%</td>
<td>62%</td>
<td>8.0 : 1</td>
</tr>
<tr>
<td>3e</td>
<td>H</td>
<td>86%</td>
<td>64%</td>
<td>- - -</td>
</tr>
</tbody>
</table>
A comparison of Tables 2 and 3 reveals an increase in yield from 10 - 20% for the D:T reactions vs the two equivalents of DIBAL case. This increase in yield is presumably due to replacement of the extra hydride equivalent with a non-hydrido alkylaluminum.

Threo N-diphenylmethylene-protected norpseudoephedrines could be easily separated from the minor (erythro) isomers via flash chromatography due to the existence of a differential Schiff base-oxazolidine tautomerism associated with compounds 3a-d (Scheme 1.14).

Schiff Base-Oxazolidine Tautomerism

Scheme 1.14

This differential tautomerism imparted a remarkable difference in polarity between the two isomers (e.g. 3a' was much less polar than 3a''). This marked difference in polarity greatly facilitated chromatographic separation of the isomers (Rf differences
were as high as 0.3 in 10% EtOAc in hexanes). Separation was also enhanced by the tendency of the *erythro* isomer to hydrolyze on silica gel. This hydrolysis was so rapid that none of the *erythro* Schiff base was actually ever isolated.

Evidence for this tautomerism is found in both the $^1$H and $^{13}$C NMR spectra of compounds 3a and 3a" (*Figures 1-4*). The $^{13}$C APT spectrum of 3a (*Figure 1*) reveals no Schiff base resonance. A quaternary peak at 99.91 ppm is consistent with an oxazolidine structure such as 3a'. The $^{13}$C APT spectrum for 3a" (*Figure 2*) shows both the imine (167.36 ppm) and the oxazolidine (99.23 ppm). The $^1$H NMR of 3a" (*Figure 3*) reveals two doublets for the C-1 methine ($\delta$ 5.0 and 4.77). These doublets integrate to approximately 1:1 (Note: 3a" was prepared from authentic (1R,2S)-norephedrine hydrochloride). The $^1$H NMR of 3a' (*Figure 4*) reveals the presence of two tautomers in a ratio of 8:1. The major tautomer is presumed to be 3a' due to the lack of Schiff base absorption in the $^{13}$C APT spectrum.

Deprotected norpseudoephedrines could be easily obtained by acid catalyzed hydrolysis of the Schiff base protecting group. Stereoselectivities were determined by $^1$H NMR after hydrolyzing an aliquot of the crude reaction mixture (the crude reaction mixture was used in order to avoid any "enhancement" of the stereoselectivity due to chromatographic purification). Stereoselectivity was clearly in the *threo* (*syn*) sense, which is consistent with the desired Cram chelation control in the C-C bond forming step (*Scheme 1.6*). A representative crude $^1$H NMR is provided (*Figure 5*).
Figure 2. $^{13}$C NMR spectrum of compound 3a.
Figure 5 - Portion of the $^1$H NMR spectrum of a hydrolyzed aliquot of crude product 3a
As stated in section 1.2, racemization of the α-center of the Schiff base ester was a potential problem. Based on O'Donnell's studies of configurational stability, it seemed likely that the center would not racemize.\textsuperscript{17a} Still, the relatively acidic pKa's of glycine, alanine, and phenylalanine Schiff base esters\textsuperscript{18} warranted a rigorous examination of the chiral integrity of the norspeudoephedrines synthesized via this method. To determine the degree of racemization associated with this method, Mosher esters were prepared in the following manner (Scheme 1.15).

\begin{center}
\includegraphics[width=\textwidth]{scheme1.15.png}
\end{center}

\textbf{Scheme 1.15}
Reagents: a. Benzoyl chloride, DMAP, Pyr; b. 2 eq PPTS, THF : H$_2$O (10:1); c. R-(+)-Mosher's acid, DMAP, DCC, CH$_2$Cl$_2$.\textsuperscript{14a,30}

Compound 3a was benzoylated using standard conditions. Hydrolysis of Schiff base 4 using 2 equivalents PPTS in THF : H$_2$O (10:1) caused the benzoyl group to migrate to form benzamide 5. Benzamide 5 was treated with R-(+)-Mosher's acid, DCC, and DMAP.\textsuperscript{14a,30} After 3 days at room temperature, compound 6 was obtained in good
yield. An aliquot of crude product was removed and analyzed by $^1$H NMR.

When the antipode of 3a (prepared from authentic (1$R$, 2$R$)-norpseudoephedrine hydrochloride) was subjected to the same procedure, 6' was obtained. Comparison of crude $^1$H NMR spectra for compounds 6 and 6' revealed 1.6% racemization (Figures 6 and 7).

Figure 6 shows overlays of the crude $^1$H NMR spectra for 6 and 6'. Clearly, protons $H_a$-$c$ have distinct chemical shifts. A small peak at $\delta$ 3.50 in the crude spectrum of 6 is due to $H_c$ from 6' ($\delta$ 3.48). Integration of both the peak at $\delta$ 3.48 and the peak at $\delta$ 3.44 reveals a 1:60 ratio which corresponds to 1.6% racemization. It is unclear at which stage of the synthesis this racemization is introduced. Garner et al. have reported that commercially available D- and L-serine (Aldrich Chemical Co.) were contaminated with approximately 1% of their respective antipodes.$^{14a}$ Assuming that the alanine starting material used in this synthesis is subject to the same degree of contamination, the norpseudoephedrine synthesis discussed in this section proceeds with approximately 0.5% racemization. Assuming that alanine is enantiomerically pure, this method provides norpseudoephedrines with 97% ee. Since the enantiomeric purity of the starting material is unknown, it can be concluded that the enantiomeric excess for this method is at least 97% if not better!
Figure 6 - Portions of the crude $^1$H NMR spectra of compounds 6 and 6' (lower trace is 6)
Figure 7 - Portions of the crude $^1$H NMR spectra of compound 6 and a 6:6' (1:1) mixture (lower trace is 6)
1.5 Stereoselective Synthesis of Sphingosines

Having established the conditions necessary for optimum yield and stereoselectivity in the norpseudoephedrine synthesis, attention was turned to synthesis of threo-sphingosine and other sphingosine analogs. As stated in Section 1.1, sphingosine is a naturally occurring \( \beta \)-amino alcohol with potent protein kinase C inhibition activity.\(^2\) This activity, coupled with the fact that sphingosine is the lipid constituent of a major class of cell surface glycoconjugates, the glycosphingolipids, has prompted a great deal of interest in stereoselective syntheses of sphingosine.\(^{12,31}\) Although D-erythro sphingosine is the naturally occurring isomer and has received the greatest attention in the synthetic literature, D-threo sphingosine is also of interest.\(^{32}\) For example, Sphinx Pharmaceutical Corp has begun clinical studies using dihydro-threo-sphingosine as their lead compound in a new treatment for psoriasis.\(^{32a}\) Tkaczuk and Thornton have proposed using \(^{13}\)C NMR to probe the effect of threo-ceramides on membrane organization.\(^{32b}\) (Ceramide is the fatty acid amide conjugate of sphingosine; see Chapter 3). N. S. Radin et al. have explored the use of threo-ceramide derivatives as glycosyltransferase inhibitors (see Chapter 4).\(^{32c}\) Their studies reveal that threo-2-decanoylamino-1-phenyl-1,3-propan-diol is a potent inhibitor of glucosyltransferase. Erythro-ceramide analogs tended to produce activity as substrates. The 3-OH was not necessary for inhibitory activity. Thus, 2-decanoylamino-1-phenylpropanol was shown to exhibit inhibitory activity. The most potent inhibitor was found to be threo-2-decanoylamino-3-morpholino-1-phenyl-1-propanol.\(^{32d}\) This inhibitor has recently been employed to decrease cellular glycosphingolipid content in a variety of systems.\(^{32e-m}\)
Since Newman's original use of the $\alpha$-amino acid serine as a chiral precursor to sphingosine,$^{12a,b}$ numerous syntheses based on this approach have appeared.$^{31}$ In the present case it was thought that a similar serine-based strategy would prove successful (Scheme 1.16).

![Diagram of D-Threo-Sphingosine and Vinyl Anion]

**Scheme 1.16**

The methodology for reducing the ester to the aldehyde oxidation state without reducing the imine was established for the norpseudoephedrines (Section 1.4); however, in order to synthesize threo-sphingosine via the proposed methodology, a suitable organometallic nucleophile was required. A common approach used by other workers employing serine as a chiral precursor involves treating a protected serinal derivative with pentadecynyllithium in THF to form an alkynyl serine aduct. The triple bond is then reduced to form the trans-alkenyl bond found in sphingosine (Scheme 1.17).
Preliminary studies (Section 1.2) had already indicated the lability of the N-diphenylmethylene moiety towards reducing agents. A strategy which did not involve reduction of an alkynyl adduct was therefore sought. The logical solution was to use a vinyl anion.

Vinyl anions can be generated via a number of methods. These methods include: (1) preparation of Grignards from vinyl halides,$^{33a,b}$ (2) transmetallation involving exchange with vinyl tin derivatives,$^{33c-e}$ (3) direct metallation$^{33f-i}$ and (4) metal-halogen exchange with vinyl halides.$^{33j-p}$ The latter method has seen a great deal of use. One drawback with the metal-halogen exchange approach is that most of these methods employ ethereal solvents (THF or Et$_2$O).$^{33j-p}$ The norpseudoephedrine synthesis developed in Section 1.4 had demonstrated a profound stereochemical
dependence on the nature of the solvent — stereoselectivities dropped from 8:1 for the PhMgBr (Et₂O) case to 3:1 for the PhMgBr (THF) case. This effect is most likely due to the increased coordinating ability of THF with respect to Et₂O. It was reasoned that even greater stereoselectivity could be achieved in the sphingosine case if coordinating solvents were avoided altogether. To this end, one of the classical methods for vinyl anion generation (2 eq tBuLi in Et₂O at -78 °C) was modified. It was found that if trans-alkenyl iodides were treated with 2 eq tBuLi in freshly distilled hexanes at room temperature, clean lithium-iodine exchange occurred to yield the corresponding alkenyllithiums. Alkenyllithiums were quenched by either benzaldehyde or D₂O in order to determine the efficiency of conversion and retention of configuration (Scheme 1.18).

\[
\begin{align*}
\text{R} \quad \text{I} & \xrightarrow{2 \ \text{tBuLi} \ \text{Hexanes}} \quad \text{R} \quad \text{Li} \\
7a \quad R = nC_4H_9 & \quad 7b \quad R = nC_5H_{11} \\
7c \quad R = nC_6H_{17} & \quad 7d \quad R = nC_{13}H_{27}
\end{align*}
\]

Scheme 1.18

Benzyl alcohols 8a-d were obtained in approximately 75% yield while the yield of trans-1-deuteropentadecene 9 was quantitative. ^1H NMR data for compound 9 revealed that stereochemical retention was complete (none of the cis isomer was observed).
Having established a convenient method for generating trans-alkenyl anions in non-coordinating solvent, Schiff base ester 1d was subjected to the protocol developed for the norpseudoephedrines replacing PhMgBr (Et₂O) with various trans-alkenyllithiums. Threeo-sphingosine derivatives 10a-d and 11a-d were obtained in excellent chemical and stereochemical yield (Table 4).³³r

\[ R\text{Me} \quad \text{Ph} \quad \text{Ph} \quad \text{OH} \]

\[ 1d \text{ or } 1f \quad 1.1 \text{ eq } D : T ; \text{CH₂Cl₂} ; -78 °C \quad 2. \text{RLi} ; -78 °C \text{ to RT} \]

\[ 10a - d \quad \text{or} \quad 11a - d \]

### Table 4

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>Yield</th>
<th>Threeo : Erythro</th>
<th>R'</th>
</tr>
</thead>
<tbody>
<tr>
<td>10a</td>
<td>H</td>
<td>78%</td>
<td>15 : 1</td>
<td></td>
</tr>
<tr>
<td>10b</td>
<td>H</td>
<td>85%</td>
<td>15 : 1</td>
<td></td>
</tr>
<tr>
<td>10c</td>
<td>H</td>
<td>72%</td>
<td>15 : 1</td>
<td></td>
</tr>
<tr>
<td>10d</td>
<td>H</td>
<td>75%</td>
<td>15 : 1</td>
<td></td>
</tr>
<tr>
<td>11a</td>
<td>TBDMOSO</td>
<td>76%</td>
<td>&gt;20 : 1</td>
<td></td>
</tr>
<tr>
<td>11b</td>
<td>TBDMOSO</td>
<td>83%</td>
<td>&gt;20 : 1</td>
<td></td>
</tr>
<tr>
<td>11c</td>
<td>TBDMOSO</td>
<td>65%</td>
<td>&gt;20 : 1</td>
<td></td>
</tr>
<tr>
<td>11d</td>
<td>TBDMOSO</td>
<td>60%</td>
<td>&gt;20 : 1</td>
<td></td>
</tr>
</tbody>
</table>
As in the nornephteine case, Schiff base protecting groups could be removed via acid catalyzed hydrolysis to provide completely deprotected \textit{threo}-sphingosines $10a'$-$d'$ and $11a'$-$d'$.

In order to establish the \textit{threo}-selectivity of this process, compounds 12a-c were synthesized (Scheme 1.19).

\begin{equation}
\text{Scheme 1.19}
\end{equation}

Compound 12a displayed a vicinal coupling constant of 7.6 Hz for the -OCH-HCN resonances. This coupling constant is \textbf{not} consistent with the empirical rules for stereochemical assignment,\textsuperscript{35} assuming that the configuration of 10a-d and 11a-d is actually \textit{threo}. Coupling constants for \textit{trans}-oxazolidinones usually range from 3 - 5 Hz. Coupling constants for \textit{cis}-oxazolidinones usually range from 6 - 8 Hz.\textsuperscript{35d} Compound 12b also showed a vicinal coupling constant for the -OCH-HCN- resonances that was inconsistent with a \textit{threo} assignment ($J = 7.7$ Hz). In light of this apparent discrepancy, Schiff base 11a was hydrolyzed to the corresponding amino diol which was acylated to provide the triacetate 12c. Compound 12c was identical in every respect.
with the known compound.\(^{35}\) Thus the *threo* assignment implicated by the norpseudoephedrine synthesis was confirmed unambiguously for sphingosines 10a-d and 11a-d.

Although the \([\alpha]_D\) for 12c was +8.2 ° indicating that racemization was approximately 3%,\(^{36}\) compound 10b was converted to its Mosher ester 15 in order to determine the exact extent of racemization. The antipode of 10b was also converted to its Mosher ester 15' (Scheme 1.20).

\[
\begin{align*}
\text{Scheme 1.20} \\
\text{Reagents: a. Benzoyl chloride, DMAP, Pyr; b. 2 eq PPTS, THF : H}_2\text{O (10 : 1); c. R-(-)-Mosher’s acid, DMAP, DCC, CH}_2\text{Cl}_2.\text{14a,30}
\end{align*}
\]
Comparison of the crude $^1$H NMR spectra for compounds 15 and 15' revealed no evidence of racemization (Figures 8 and 9). Figure 8 shows the crude $^1$H NMR spectrum of compounds 15 and 15'. The resonances of interest have been labeled a-e. The $H_a$ resonances for these compounds absorb too closely to really achieve any clear indication as to the extent of racemization. This is also true of the $H_e$ resonances (15 $\rightarrow$ 3.53 ppm; 15' $\rightarrow$ 3.51 ppm). However, analysis of the $H_d$ resonances clearly shows no presence of 15 in the spectrum of 15' ($H_d$ for 15 absorbs from 5.97 to 5.88 ppm).

Perhaps even more telling are the resonances due to $H_b$ and $H_c$. These resonances overlap and occur from 5.59 to 5.49 ppm for 15 and from 5.50 to 5.36 ppm for 15'. Analysis of the spectrum of 15' (Figure 8) reveals no trace of 15. Thus, analysis of two different resonances clearly shows that no contamination (either 15 with 15' or 15' with 15) can be detected using this method. Based on the norpseudoephedrine results (Figures 6 and 7) it is concluded that the threo-sphingosine synthesis proceeds with $\leq$ 1.6 % racemization! A "spiked" spectrum consisting of essentially equimolar amounts of both 15 and 15' (Figure 9) indicates how clearly the $H_b$, $H_c$, and $H_d$ resonances from both diastereomers may be distinguished when in a mixture.
Figure 8 - Portions of $^1$H NMR spectra for compounds 15 and 15'
Figure 9 - Portion of the $^1$H NMR spectrum of an equimolar mixture of 15 and 15'
T. Ibuka et al. have reported a one-pot method for converting Boc-protected α-amino esters to β-amino alcohols. Their method is similar to the method discussed in this chapter. It differs from the present method, however, in that DIBAL is used as the sole reducing agent and the nucleophile is not added until the aldehyde has been generated in situ (i.e. Grignard is not added until after the DIBAL/amino ester mixture has been warmed to -20 °C for 0.5 h, which presumably generates the aldehyde). Stereoselectivities as high as > 15:1 (syn:anti) are obtained when vinylmagnesium chloride is used as a nucleophile. Vinylmagnesium bromide provided a 2:1 mixture of allylic alcohols in very low yield. Based on these results, the N-diphenylmethylene protecting group appears to be comparable to Boc in terms of stereocontrol when Grignards are used as nucleophiles. This comparison is not rigorous however since Ibuka’s results are based on vinyl Grignards and not phenyl Grignards.

In order to better assess the efficacy of the Schiff base protecting group relative to the more common Boc protection, compound 16 was subjected to the one-pot protocol developed in this chapter (Scheme 1.21).

Scheme 1.21

When 16 was treated with D:T at -78 °C followed by trans-pentadecenyllithium (R'Li), an inseparable mixture of both syn and anti isomers of 17 was obtained. Integration of the four diastereomeric vinyl resonances in the 13C NMR indicated the stereoselectivity (after chromatography) to be 6.4:1 (Figure 10).
Figure 10 - Portion of the $^{13}$C NMR spectrum of compound 17
Clearly, the N-diphenylmethylene protecting group is superior to Boc in terms of stereoselectivity when the D:T protocol is followed. In addition, the diastereomeric products are more easily separated by chromatography. Chromatographic separation of the isomeric sphingosines formed from 1d is facile due to the Schiff base-oxazolidine tautomerism discussed earlier. In contrast, the isomers of 17 were not separated by this method. The Schiff base ester analogous to 16 is 1d. Compound 1d is superior to 16 in terms of ease of preparation, crystallinity, and stability. Compound 16 is an oil and therefore more difficult to manipulate than the crystalline 1d. Introduction of the Boc group is a straightforward process but is technically more complicated than introduction of the Schiff base (i.e.-Boc protection is typically performed under reflux and purification often requires chromatography, in contrast to the benzophenone Schiff base which is conveniently introduced at RT and usually produces very clean crystalline crude products that if necessary can be purified via simple recrystallization).
1.6 Conclusion

A new method for stereoselective synthesis of β-amino alcohols has been developed. This method is similar to other methods in that it depends on the chirality inherent in α-amino acids as a means of establishing stereocontrol during 1,2-carbonyl addition. It differs from other methods in that a new amino protecting group is employed, i.e. the N-diphenylmethylene protecting group first introduced by O'Donnell. The Schiff base esters used as starting materials for this method possess the following characteristics:

(1) They are easily synthesized from readily available α-amino esters and diphenylketimine.
(2) They are highly crystalline. This crystallinity greatly facilitates purification and manipulation (i.e. weighing, transfer etc).
(3) They are extremely stable. Schiff base esters may be stored for months at room temperature in a dessicator with no sign of decomposition.
(4) They are configurationally stable under both acidic and mildly basic conditions.
(5) The Schiff base nitrogen possesses a lone pair of electrons. This lone pair may be involved in chelation and thus participate in the stereochemical outcome of a reaction.
(6) The diphenylmethylene bond is inert toward PhMgBr and various alkenyllithiums. It is reduced by DIBAL only after the more reactive ester moiety is reduced. It is labile to LiBH₄ reduction.

These characteristics, taken together, make the N-diphenylmethylene-protected α-amino esters very attractive starting materials for β-amino alcohol syntheses.

In addition to the qualities of the starting materials discussed above, the method described in this chapter possesses the following salient characteristics:

(1) A wide variety of β-amino alcohols may be synthesized, depending on the α-amino ester and nucleophile used.
(2) The method is highly threo-selective (stereoselectivities ranged from 8:1 to > 20:1).
(3) The stereoisomers are easily separated via chromatography due to a differential Schiff base-oxazolidine tautomerism.

(4) The products are obtained in enantiomerically enriched form (> 97% ee).

(5) The Schiff base protecting group may be easily removed via acid catalyzed hydrolysis to yield unprotected threo $\beta$-amino alcohols.

The method described in this chapter complements existing methods by capitalizing on the ready availability of optically pure $\alpha$-amino acids while at the same time improves on existing methodologies by providing a solution to the longstanding problem of configurational instability. Thus, this method constitutes a novel and extremely useful contribution to the field of $\beta$-amino alcohol synthesis in particular and synthetic methodology in general.
CHAPTER 2

MECHANISTIC STUDIES OF SEQUENTIAL REDUCTION/C-C BOND FORMATION
2.1 Introduction

Since its introduction in 1958, \( \text{diisobutylaluminum hydride (DIBAL)} \) has proven to be virtually indispensable as a reagent for organic synthesis. Although DIBAL is useful in a variety of reactions, its most common use has been in the selective reduction of esters to aldehydes. This selective reduction is possible due to the relative stability of the intermediate that is formed (Scheme 2.1).

![Scheme 2.1](image)

**Scheme 2.1**

It has been postulated that the strength of the Al-O bond in \( \text{I} \) inhibits expulsion of the alkoxide ion and thus prohibits further reduction of the aldehyde to form the \( 1^\circ \) alcohol (Scheme 2.2).

![Scheme 2.2](image)

**Scheme 2.2**
Some authors\textsuperscript{40a} have claimed that intermediate I is stable enough that aldehyde is not liberated until hydrolytic work-up, while others have invoked coordinated aldehyde II as being a reactive intermediate even at low temperatures.\textsuperscript{15} Recently, Kiyooka and Shirouchi invoked structure I as the reactive intermediate leading to aldol product (Scheme 2.3).\textsuperscript{40c}

\[
\begin{aligned}
\text{DIBAL, -78 °C} & \quad \text{BF}_3 \cdot \text{Et}_2\text{O} \\
\text{I} & \quad \text{II}
\end{aligned}
\]

Scheme 2.3

Stable tetrahedral intermediates similar to I have been reported in a number of cases (Scheme 2.4).\textsuperscript{41} The tetrahedral intermediates shown in Scheme 2.4 have been invoked to explain the observed addition of only one equivalent of organometallic reagent to the starting carboxylic acid derivatives. These explanations seem reasonable since, in the absence of Lewis acid, acetals are known to be inert toward organometallic nucleophiles.\textsuperscript{42} Since all of the intermediates shown in Scheme 2.4 are similar in structure to acetals it is reasonable to expect them not to undergo further addition of organometallic reagent.

The existence of I as a reactive intermediate (Scheme 2.3) is supported by the fact that in the presence of a Lewis acid, acetals undergo reaction with a variety of nucleophiles.\textsuperscript{43-47} A recent review provides details for over 70 examples of Lewis acid-mediated acetal reactions.\textsuperscript{43} The reaction of acetals with silicon-containing nucleophiles (such as the silyl ketene acetal shown in Scheme 2.3) has proven to be a very useful method for C-C bond formation.
Examples of silicon-containing nucleophiles used in these reactions include: (1) allylsilanes,44 (2) enol silanes,45 (3) TMS-CN46 and (4) silyl acetylenes.47

Lewis acid-mediated addition of allylsilanes to chiral acetals has been used to synthesize a variety of target molecules with good to excellent stereoselectivity. For example, when IV was treated with 2-methylallylsilane and a 6:5 mixture of TiCl₄ and Ti(OiPr)₄, compound V was obtained in 94% chemical yield with 97% ee (Scheme 2.5).
Scheme 2.5

Johnson et al. have employed chiral acetals in the stereoselective synthesis of several (3S,4S) and (3S,4R) statine derivatives (Scheme 2.6).44r

(a) \((R_1 = \text{iBu}, R_2 = \text{H})\)

(b) \((R_1 = \text{H}, R_2 = \text{iBu})\)

Scheme 2.6
Kozikowski and Sorgi\cite{44} have reported the stereoselective synthesis of C-glycosides via a Lewis acid-mediated allylsilane addition to 1-O-Acetyl glycosides (Scheme 2.7).

\begin{equation}
\text{ZnBr}_2 + \text{OTBDMS OTBDMS OTBDMS} (4:1)
\end{equation}

\textbf{Scheme 2.7}

Lewis acid-mediated addition of enol silyl ethers to acetals has also been used in a variety of syntheses. For example, the carbon framework of texanetriene, an intermediate in the synthesis of the powerful anti-tumor compound taxol, was constructed by this reaction (Scheme 2.8).\cite{43}

\textbf{Scheme 2.8}
Successful intramolecular TiCl₄ mediated aldol reactions of silyl enol ethers with acetals have been reported (Scheme 2.9).⁴⁵ᵐ

Scheme 2.9

Other attempts to affect this ring closure using a variety of acidic and basic reaction conditions failed to give the desired aldol product. One of the chief advantages of this route is that the aldol adduct is not susceptible to a reverse aldol reaction.⁴⁵ᵐ Johnson et al. have reported stereoselective addition of acetone trimethylsilane enol ether to chiral acetal VI (Scheme 2.10).⁴⁵ⁿ

Scheme 2.10

<table>
<thead>
<tr>
<th>R</th>
<th>Yield</th>
<th>Vla:Vlb</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂=CHCH₂CH₂</td>
<td>93%</td>
<td>96:4</td>
</tr>
<tr>
<td>cyclohexyl</td>
<td>90%</td>
<td>97:3</td>
</tr>
<tr>
<td>C₈H₁₇</td>
<td>84%</td>
<td>99:1</td>
</tr>
</tbody>
</table>
Addition of silyl nitriles to chiral acetals via TiCl₄ catalysis yields adducts VIIa and VIIIb in excellent yield and with a high degree of stereoselectivity (Scheme 2.11).⁴⁶c

\[ \text{R R} \text{O} \text{CN} \xrightarrow{\text{TMS-CN}} \text{R} \text{O} \text{CN} \xrightarrow{\text{TiCl₄, CH₂Cl₂, -78 °C}} \text{VIIa} + \text{VIIIb} \]

(100% yield, VIIa:VIIIb = 97:3)

**Scheme 2.11**

Cleavage of the pentane-2,4-diol followed by reduction of the nitrile yields the corresponding β-amino alcohol in good yield.⁴⁶c

The TiCl₄ catalyzed addition of silyl acetylenes to chiral acetals is also stereoselective (Scheme 2.12).⁴⁷a

\[ \text{R R'} \text{HO} \xrightarrow{\text{Me₃Si-≡-R'}} \text{R} \text{HO} \xrightarrow{\text{TiCl₄, CH₂Cl₂, -78 °C}} \text{R} \text{HO} + \text{R'} \text{HO} \]

Chemical yield: 80-98%
Stereoselectivity: 86:14 to 97:3

**Scheme 2.12**

Interestingly, chiral acetals may also be cleaved by organoaluminum reagents (in the absence of any additional catalyst) to yield optically active 2° alcohols (Scheme 2.13).⁴⁸
In light of both the number of stable acetal-like intermediates reported in the literature (Scheme 2.4)\textsuperscript{41} and the many examples of Lewis acid-catalyzed addition of nucleophiles to acetals,\textsuperscript{43-48} a reaction pathway involving Lewis acid-catalyzed addition of a nucleophile to an aluminoxy-acetal such as structure I (Scheme 2.3) is quite plausible. Indeed, Kiyooka and Shirouchi have invoked just such a mechanism for the Lewis acid-catalyzed addition of silylketene acetalts to aluminoxy acetals. In the threo-selective $\beta$-amino alcohol synthesis developed in Chapter 1, an N-diphenylmethylene-protected $\alpha$-amino ester is treated with D:T and an organometallic reagent at -78 °C. This procedure was shown to proceed with $\leq$ 1.6% racemization of the $\alpha$ center. It seemed likely that an aluminoxy-acetal similar to structure I might be the reactive intermediate in this reaction, rather than an aldehyde (aldehydes have lower pKa's than esters or aluminoxy-acetals, and would therefore be expected to racemize much more readily), and that this intermediate might undergo a Lewis acid-catalyzed addition of organometallic reagent similar to the examples provided above (Scheme 2.14).
Scheme 2.14
Implicit in Scheme 2.14 is the fact that there are two mechanistic extremes for Lewis acid catalyzed addition of nucleophiles to acetals: (1) an $S_N^2$-like mechanism where C-O bond breakage coincides with C-Nu bond formation or (2) an $S_N^1$-like mechanism where C-O bond breakage occurs prior to formation of the C-Nu bond, and thus involves an oxocarbonium ion (Scheme 2.15).

**Scheme 2.15**

Due to the high degree of stereoselectivity associated with the chiral acetal reactions reviewed above (Schemes 2.5 - 2.13) a great deal of attention has been devoted to elucidating the mechanism involved.\(44o,p,q,45o,48b,49\) Essentially three different mechanistic rationalizations have been put forth. These rationalizations differ only in the timing and extent of C-O bond breakage and C-C bond formation.\(49e\) The three postulated mechanisms include: (1) nucleophilic attack of a separated ion pair ($S_N^1$-like)\(44o,p,45o,48b,c\) (2) nucleophilic attack of a tight ion pair ($S_N^1$-like) and (3) Lewis acid-assisted nucleophilic attack of the partially intact acetal ($S_N^2$-like).\(44q,46d,48b\)
Nucleophilic $S_N 1$-like attack of a separated ion pair has been invoked by several authors. In 1981 both Richter and H. Yamamoto et al. reported the stereoselective reduction of chiral acetals by aluminum hydrides (Scheme 2.13). Both authors proposed that a preferential Lewis acid-acetal complex is formed, and that following C-O bond cleavage, hydride is delivered internally to provide $2^\circ$ alcohols with good stereoselectivity (Scheme 2.16).

**Scheme 2.16**

P. A. Bartlett and W. S. Johnson were the first to propose a $S_N 1$-like tight ion pair mechanism (Scheme 2.17). The origin of the stereoselectivity in Scheme 2.17 was postulated to be due to
preferential reaction of the least sterically congested ion pair \( (X) \). Heathcock et al. and Denmark and Almstead have also invoked tight ion pairs.

Scheme 2.18

The Lewis acid-assisted \( S_N^2 \)-like mechanism was first postulated by Johnson (Scheme 2.18). Reaction path "a" is favored over "b" due to the relief of the 2,4-diaxial interaction in transition state XIV leading to product. The 2,4-diaxial interaction persists through reaction path "b", thus transition state XV is higher in energy than XIV, and, as a result, is energetically less favorable.

It is not clear which of these three mechanistic possibilities is predominant. Indeed, many authors have reported a mechanistic divergence, the mechanism depending on such things as acetal structure, solvent, temperature, and characteristics of the Lewis acid and/or nucleophile.
2.2 Stereochemical Influence of the Steric Bulk of the Ester Moiety

In order to determine which of the two mechanistic extremes (Scheme 2.14) was operating in the threo-selective β-amino alcohol synthesis developed in Chapter 1, a series of Schiff base esters was synthesized (Table 5).

![Reaction Scheme]

Table 5

<table>
<thead>
<tr>
<th>Compound</th>
<th>R'</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Et</td>
<td>80%</td>
</tr>
<tr>
<td>1f</td>
<td>CH₃</td>
<td>80%</td>
</tr>
<tr>
<td>1g</td>
<td>PhCH₂</td>
<td>80%</td>
</tr>
<tr>
<td>1h</td>
<td>Ph₂CH</td>
<td>81%</td>
</tr>
<tr>
<td>1i</td>
<td>tBu</td>
<td>80%</td>
</tr>
</tbody>
</table>

It was reasoned that if the reaction proceeded via a separated ion S_N1-like mechanism, the steric bulk of the ester should have no influence on the stereochemical outcome of the reaction (Scheme 2.14) since the alkoxide would be completely dissociated at the time of nucleophilic attack. If either a tight ion S_N1-like or Lewis acid-assisted S_N2-like mechanism were followed, the steric bulk of the ester should exert some influence on the stereochemical outcome of the reaction.
When esters 1a-f-i were treated with D:T and PhMgBr at -78 °C the following results were obtained (Table 6). The bulk of the ester clearly influenced the stereochemical outcome of the reaction when PhMgBr in either Et₂O or Et₂O : THF (1:1) were used as nucleophiles. As already discussed in Chapter 1, the presence of THF lowered the stereoselectivity. In spite of this decreased stereoselectivity, a correlation between steric bulk and stereoselectivity was observed (Table 6).

![Chemical structure](image)

**Table 6**

<table>
<thead>
<tr>
<th>Compound</th>
<th>R'</th>
<th>Syn : Anti</th>
<th>Syn : Anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>1f</td>
<td>CH₃</td>
<td>7.6 : 1</td>
<td>2.7 : 1</td>
</tr>
<tr>
<td>1a</td>
<td>Et</td>
<td>8.8 : 1</td>
<td>2.6 : 1</td>
</tr>
<tr>
<td>1g</td>
<td>PhCH₂</td>
<td>6.3 : 1</td>
<td>2.6 : 1</td>
</tr>
<tr>
<td>1h</td>
<td>Ph₂CH</td>
<td>10.7 : 1</td>
<td>3.2 : 1</td>
</tr>
<tr>
<td>1i</td>
<td>tBu</td>
<td>11.0 : 1</td>
<td>3.8 : 1</td>
</tr>
</tbody>
</table>

a. In Et₂O, b. In THF:Et₂O (1:1)

These results unambiguously rule out the possibility that a separated ion pair is the reactive intermediate in this reaction. However, the distinction between a tight ion SN₁-like and a Lewis acid-assisted SN₂-like mechanism remains unclear. In either case, the steric bulk of the ester would be expected to exert some influence on the stereoselectivity of the reaction.
2.3 Trapping Intermediate VIII. Monosilyl Acetals 18a and 18b

As stated in the introduction to this chapter, it has been known for sometime that the ability of DIBAL to reduce an ester to an aldehyde without further reduction to the alcohol is due to the stability of the tetrahedral intermediate I (Scheme 2.1). Although the tetrahedral intermediate has been invoked by a number of authors, no spectroscopic or stereochemical data exist which definitively demonstrate the stability of this intermediate. In an effort to help distinguish between the two possible mechanistic pathways (i.e. $S_N$1-like vs $S_N$2-like) and in order to establish a reference point for the stability and longevity of the tetrahedral aluminoxy-acetal, intermediate VIII (Scheme 2.14) was trapped as its monosilyl-acetal 18a and its diastereomer 18b (Scheme 2.19).

\[ \text{Scheme 2.19} \]

It is interesting to note that although reduction of aliphatic esters to aldehydes with DIBAL is rapid (approximately 1 hour at -78 °C), compound 1a required 72 hours for complete reduction with 1.1 eq D:T at -78 °C (see Chapter 5). When this reduction was carried out using a preformed "ate" reducing agent (prepared by mixing equimolar amounts of DIBAL, TRIBAL and PhLi in dry hexanes) the reaction was much more rapid (reduction was complete after 1 hour at -78 °C) and less stereoselective (Scheme 2.20). "Ate" complexes similar to the one used in Scheme 2.20 are known to be powerful reducing agents. Since the threo-selective amino alcohol synthesis developed in Chapter 1 only requires from 15 minutes to one
hour to go to completion, it seems likely that D:T is **not** the kinetically active reducing agent in this reaction (reduction with D:T alone required 72 hours at -78 °C). Instead, an "ate" complex generated *in situ*, after DIBAL:TRIBAL:substrate chelation is complete, is most likely the kinetically active reductant (Scheme 2.21).

That chelate formation is complete prior to "ate" formation is borne out not only in the mechanics of the reaction (i.e. D:T is added to the substrate first and allowed to react 15 or 20 minutes before adding PhMgBr), but also by the fact that stereoselectivity in the pre-formed "ate" mediated reduction/silyl acetal formation is much lower (2:1) than the stereoselectivity of the norpseudoephedrine synthesis (8:1).

That monosilyl-acetals 18a and 18b can be synthesized indicates that aluminoxy-acetal VIII (Scheme 2.14) is indeed long lived (3 days at -78 °C) and therefore stable enough to be invoked realistically as a reactive intermediate. Whether or not the reaction with nucleophiles proceeds via an $S_N$1-like or an $S_N$2-like mechanism is unclear. That the stereoselectivity for the reduction step is 6.5:1 rather than 10:1 or greater implies that the mechanism is not strictly $S_N$2 (one would expect the stereoselectivity of the reduction, as reflected in the ratio of 18a:18b, to be expressed in the norpseudoephedrine and sphingosine products if the mechanism proceeds with inversion as it would in an $S_N$2-like mechanism).
Scheme 2.21
2.4 Conclusion

The mechanism of C-C bond formation in the threo-selective β-amino alcohol synthesis has been examined. Based on analogy to similar reactions reported in the literature,\textsuperscript{41,43-48} it was postulated that the reaction proceeds via an aluminoxoy-acetal intermediate, and that this intermediate might suffer nucleophilic addition via a mechanism bounded by one of two limiting extremes: (1) separated ion $S_N^1$-like or (2) $S_N^2$-like. The postulated aluminoxoy-acetal intermediate was indeed stable enough to be trapped and isolated as its monosilyl-acetal derivative $18a,b$. The stereoselectivity for the reduction step was found to be 6.5:1 ($18a:18b$)\textsuperscript{51} when D:T was used as reducing agent. When an "ate" complex prepared from DIBAL:TRIBAL:PhLi (1:1:1) was used as reducing agent, stereoselectivity was 2:1 ($18a:18b$). The D:T reduction required approximately 3 days at -78 °C to reach completion while the "ate" complex reduction only required 1h.

The stereoselectivity of the β-amino alcohol synthesis was shown to be influenced by both the solvent and the bulk of the ester moiety. Whether or not the reaction proceeds via a tight ion $S_N^1$-like or an $S_N^2$-like mechanism remains unclear. However, the dependence of the stereoselectivity on the steric bulk of the esters is evidence that a separated ion $S_N^1$-like mechanism is not involved in this chemistry.
CHAPTER 3
SYNTHESIS OF $C_{13:1}$ THREE- AND ERYTHRO-CERAMIDES
3.1 Introduction

Ceramide is the fatty acid amide of the amino diol sphingosine (Scheme 3.1). It is found in all vertebrate life forms and is important biologically due to the central role it plays in the biosynthesis of glycosphingolipids (Scheme 3.2).

**Biosynthesis of Neutral Glycosphingolipids**

![Scheme 3.1]

**Scheme 3.2**

Glycosphingolipids are cell surface oligosaccharides linked to ceramide via a glycosidic bond. As components of the cell membrane, glycosphingolipids play a vital
role in membrane organization. They also play an important role in many molecular recognition processes which occur at the cell surface. For example, glycosphingolipids have been implicated as receptors for hormones, toxins, interferon, and more recently, HIV-1 in CD-4 negative cell lines. In addition to their role as molecular receptors, glycosphingolipids are involved in one of the best studied events in surface membranes of cells undergoing viral transformation to malignancy. During this transformation, the membrane's glycosphingolipid pattern changes markedly. This marked change contributes to loss of contact inhibition of cell growth, altered surface charge, and changed aglutinability.

Both the fatty acid chain length and the chain length of the sphingosine components of ceramide are highly variable (Scheme 3.3).

Scheme 3.3

Karlsson has reported over 60 naturally occurring sphingosines. These sphingosines differ in: (1) carbon chain length (R' = C12 - C24), (2) number and configuration of double bonds (cis and trans) and (3) branching of the carbon chain. This variability seems to be both species and tissue specific. The majority of glycosphingolipids isolated from central nervous tissue of warm-blooded mammals is of the composition R' = C15:1 (i.e. R' is 15 carbons long with one double bond occurring at position 1 of R'). Gangliosides (sialic acid-containing glycosphingolipids) in warm-blooded mammals have about an equal composition of C20:1 and C18:1 (R' = C17:1, C15:1) sphingosine. The R group of ceramide (Scheme 3.3) is also highly species and tissue dependent. For example, unsaturated fatty acids are almost absent in gangliosides of warm-blooded mammals. Cold-blooded animals have
lower amounts of \( C_{18:0} \) and higher amounts of \( C_{16:0} \) fatty acids than do warm-blooded mammals.\(^{56h}\) Fatty acid composition for ceramides isolated from kidney,\(^{56b,c}\) liver\(^{56k}\) and spleen\(^{56a}\) are all markedly different.

Different chain lengths of both the fatty acid and sphingosine base of ceramide have been shown to influence its reactivity towards various enzymes \textit{in vitro}.\(^{57,58}\) For example, N-acetyl-\textit{threo}-ceramide (\( R = C_{1:0}, R' = C_{15:1} \)) is an active acceptor of phosphorylcholine and stimulates incorporation of choline into sphingomyelin.\(^{57a}\) In the absence of detergent, the N-acetyl derivative was most reactive. (Interestingly, the \textit{erythro} isomer is only 10\% as reactive as the \textit{threo} isomer!\) In the presence of 5 mg/mL of Tween 20, an 8-carbon fatty acid was most effective (\( R = C_{7:0}, R' = C_{15:1} \)). N-palmityl \textit{threo}-sphingosine (\( R = C_{15:0}, R' = C_{15:1} \)) was completely unreactive. All of the longer-chain fatty acids studied were also unreactive.\(^{57a}\) This effect was most likely due to unfavorable solubility properties associated with the long-chain ceramides.\(^{57}\) Several mammalian tissues are known to catalyze \textit{in vitro} incorporation of CDP-ethanolamine into ceramide phosphorylcholine. The activity is greater for N-octyl ceramides in this reaction than it is for the N-acetyl derivative.\(^{57b}\) Again, this difference in reactivity is most likely due to different solubility properties.

Interest in synthesizing ceramides with various chain lengths has arisen due to this solubility induced difference in reactivity. Several studies have appeared which report either an increase in reactivity\(^{58a}\) or enhanced tractability\(^{58b}\) for cerebroside synthetase-catalyzed glycosidations of short-chain ceramides. These enhanced properties of the short-chain ceramides have led to the development of more sensitive and efficient assays for cerebroside synthetase activity.\(^{58}\)

Due to this recent interest in short-chain ceramides, and in order to extend the scope of the \textit{threo}-selective sphingosine synthesis developed in Chapter 1 to include \textit{erythro}-ceramides, a synthesis of \( C_{13:1} \) \textit{erythro}-ceramide was undertaken.
3.2 Attempted Mitsunobu Inversion of N-Diphenylmethylene-Protected β-Amino Alcohols

In order to extend the *threo*-selective synthesis of β-amino alcohols to include *erythro*-ceramides, a method for inverting the 3-OH was necessary (Scheme 3.4).

![Scheme 3.4](image)

A common approach to this problem involves Mitsunobu inversion of a suitably protected *threo*-sphingosine (Scheme 3.5).37

![Scheme 3.5](image)

Ito et al.37
Reagents: 2 Ph3P, 2 PhCO2H, 2 DEAD

Scheme 3.5

In the present case it was hoped that a similar protocol would yield 3-O-acyl-N-diphenylmethylene-protected *erythro*-sphingosines that could then be deprotected and N-acylated to yield the desired ceramide (Scheme 3.6).
Scheme 3.6  Reagents: a) 2 P₃H, 2 RCO₂H, 2 DEAD; b) H₃O⁺; c) Stearyl Chloride; d) NaOMe/MeOH.

In order to explore the feasibility of this protocol, Schiff base 3a was subjected to Mitsunobu inversion using a variety of reaction conditions. Unfortunately, none of the desired product was ever isolated (Scheme 3.7).

Scheme 3.7

It was postulated at this point that the failure of 3a to react in the Mitsunobu reaction was due to the Schiff base-oxazolidine tautomerism noted in Chapter 1 (Scheme 3.8).
Since the 3a-3a' equilibrium lies far to the right, it was not too surprising that 3a' did not react under typical Mitsunobu conditions. It is even less surprising that no reaction occurred if one considers that the oxazolidine ring may be protonated by one of the two equivalents of \( RCO_2H \) employed in standard Mitsunobu reactions, thereby trapping 3a as the unreactive 3a' (Scheme 3.9).

### Scheme 3.9

In order to avoid the potential problem created by protonating 3a', the Mitsunobu
reaction was repeated replacing $\text{RCO}_2\text{H}$ with $\text{RCO}_2\text{Cs}$ (Scheme 3.10).

Scheme 3.10

Cesium carboxylates are known to be good nucleophiles. The large polarizable cesium ion leads to an enhanced carboxylate nucleophilicity not exhibited by other carboxylate salts ($\text{RCO}_2\text{Na}$, $\text{RCO}_2\text{K}$ and $\text{RCO}_2\text{Rb}$). By replacing $\text{RCO}_2\text{H}$ with $\text{RCO}_2\text{Cs}$ it was hoped that this enhanced nucleophilicity together with the lack of an acidic proton (to avoid protonating 3a') would lead to desired product. Unfortunately this approach also failed and none of the desired product was obtained. However, when the diastereomer 3a'' was subjected to this same cesium carboxylate protocol, *threo* product 19 was obtained in 23 - 37% yield (Scheme 3.11).
That *erythro* 3a'' can be successfully converted to 19 via a modified Mitsunobu reaction while 3a cannot is further evidence that 3a is unreactive due to the Schiff base-oxazolidine tautomerism.

Thus, extension of the *threo*-selective Schiff base alcohol synthesis developed in Chapter 1 to include *erythro* isomers was unsuccessful via either standard or modified Mitsunobu inversion chemistry as long as the amino group retained its diphenylmethylene protection.
3.3 Mitsunobu Inversion of a Threo N-Acyl β-Amino Alcohol to Provide C$_{13}$:1 Erythro-Ceramide

Having found that Schiff base-protected threo β-amino alcohols could not be converted to the erythro isomer via the standard Mitsunobu protocol and a modified Mitsunobu technique, an alternate method for inversion of the 3-OH was sought. Since there is ample precedent for inversion of N-acyl amino alcohols via the Mitsunobu reaction,\textsuperscript{12d,37} a strategy involving an N-acyl sphingosine derivative was explored. In order to determine the optimum conditions for ultimate conversion of 11b to C$_{13}$:1 ceramide, the model reactions outlined in Scheme 3.12 were performed. When (1$R$,2$R$)-norpseudoephedrine was treated with 20 and HOBT (cat) in pyridine, N-acetyl-norpseudoephedrine 21 was obtained. The hydroxyl was then inverted using standard Mitsunobu chemistry to provide 22. In order to determine that the erythro isomer had indeed been formed, compound 21 was acylated with pivaloyl chloride to provide 23. Comparison of the $^1$H NMR spectra of 22 and 23 reveals that they are clearly distinct compounds (see Chapter 5). Since 23 was obtained via a method known to proceed without inverting the hydroxyl center, and since 22 is clearly different from 23, compound 22 must have the erythro configuration as shown (Scheme 3.12).
OH
(1R, 2R)-Norpseudoephedrine

\[
\begin{align*}
\text{HOBT (cat), Pyr; b) 2 \text{ Ph}_3\text{P}, 2 \text{ DEAD, 2 Pivalic Acid; c) Pivaloyl Chloride, Pyr}}
\end{align*}
\]

These model reactions, coupled with the literature precedent for Mitsunobu inversion of N-acyl \( \beta \)-amino alcohols,\textsuperscript{12d,37} firmly established the feasibility of synthesizing \( \text{C}_{13:1} \) erythro-ceramide from an N-acyl derivative of \( 11\text{b} \). In order to synthesize such a derivative, an efficient method for cleaving the Schiff base of \( 11\text{b} \) without simultaneously cleaving the TBDMS protecting group was needed (Scheme 3.13).

Scheme 3.12

To determine appropriate conditions for effecting this transformation, TLC experiments were performed with Schiff base ester \( 1\text{d} \). Eventually it was found that treatment of

Scheme 3.13
1d with 2 equivalents of PPTS in THF : H₂O (10:1) resulted in clean cleavage of the Schiff base without cleaving the TBDMS group (Scheme 3.14).

Scheme 3.14

Although this process appeared quantitative by TLC when applied to compound 1d (none of the completely deprotected methyl serinate was detected), when applied to compounds 11a and 11b on a preparative scale, products 24 and 25 were obtained in only approximately 50% yield (Scheme 3.15).

Scheme 3.15

This isolated yield of 24 and 25 was unexpectedly low, based on the TLC experiment conducted above. Since isolation of compounds 24 and 25 was accomplished via
chromatography using MeOH/CH$_2$Cl$_2$ as eluent, it is reasonable to assume that this low yield is due to hydrolysis of the TBDMS group on the SiO$_2$ column in the presence of the very polar solvent system.

Having compound 24 in hand, it was subjected to the chemistry developed for the model system (Scheme 3.16).

Scheme 3.16 Reagents: a) HOBT (cat), pyr; b) 2 Ph$_3$P, 2 DEAD, 2 Pivalic acid; c) Pivaloyl Chloride, DMAP (cat), pyr; d) NaOMe/MeOH, reflux 24 h.
Compound 24 could be cleanly N-acylated to provide 27 by reaction with 26 (R = C\textsubscript{17}H\textsubscript{35}), and HOBT (cat) in pyridine. Compound 27 could be converted to either C\textsubscript{13:1} threo-ceramide 31 or C\textsubscript{13:1} erythro-ceramide 30. The \textsuperscript{1}H NMR spectra for compounds 28 and 29 showed the expected resonances. Since 28 was obtained via a process which does not involve inversion of the C-3 hydroxyl and since 29 is clearly different from 28 by \textsuperscript{1}H NMR, 29 must have the erythro configuration. Fully deprotected C\textsubscript{13:1} ceramides were obtained by refluxing 28 and 29 with NaOMe and MeOH.
3.4 Conclusion

A convenient method for converting threo-N-diphenylmethylene-protected sphingosines to either threo- or erythro-ceramides has been developed. Direct Mitsunobu inversion of the Schiff base protected sphingosines to provide the erythro isomer was not possible using a variety of conditions. Experiments suggest that this lack of reactivity is due to the Schiff base-oxazolidine tautomerism. In order to accomplish the desired 3-OH inversion, the Schiff base had to be removed and replaced with an N-acyl protecting group. This N-acyl-threo-sphingosine was then easily inverted to provide erythro-ceramide using standard Mitsunobu methodology.

Although the method developed in this chapter was performed using a short-chain sphingosine (C_{13:1}), all of the threo-sphingosines synthesized in Chapter 1 (Table 4) could be subjected to this methodology. Both the C_{13:1} threo- and erythro-ceramides, and other shorter-chain ceramides potentially derived from compounds 11c,d could be used to develop potentially more efficient or more sensitive cerebroside synthetase assays. In addition, the more common naturally occurring C_{18:1} ceramides could be synthesized from compound 25 following the chemistry developed for 24.
CHAPTER 4
N-DIPHENYLMETHYLENE-PROTECTED SPHINGOSINES AS GLYCOSYL ACCEPTORS: β-SELECTIVE GLYCOSYLATION (C-O BOND FORMATION) VIA A FAVORABLE SCHIFF BASE-HYDROGEN BONDING PATTERN
4.1 Introduction

Scheme 4.1
As stated in the introduction to Chapter 3, glycosphingolipids are cell membrane components composed of various oligosaccharides bound to ceramide via a glycosidic bond (Scheme 4.1). Several classes of glycosphingolipids with different carbohydrate core structures have been characterized (Table 7).

Table 7

<table>
<thead>
<tr>
<th>Prefix</th>
<th>Core Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lacto</td>
<td>Gal(β1→3)GlcNAc(β1→3)Gal(β1→4)Glc</td>
</tr>
<tr>
<td>Lactoneo</td>
<td>Gal(β1→4)GlcNAc(β1→3)Gal(β1→4)Glc</td>
</tr>
<tr>
<td>Muco</td>
<td>Gal(β1→3)Gal(β1→4)Gal(β1→4)Glc</td>
</tr>
<tr>
<td>Gala</td>
<td>GalNAc(α1→3)GalNAc(β1→4)Gal(α1→4)Gal</td>
</tr>
<tr>
<td>Globo</td>
<td>GalNAc(β1→3)Gal(α1→4)Gal(β1→4)Glc</td>
</tr>
<tr>
<td>Globoiso</td>
<td>GalNAc(β1→3)Gal(α1→3)Gal(β1→4)Glc</td>
</tr>
<tr>
<td>Ganglio</td>
<td>Gal(β1→3)GalNAc(β1→4)Gal(β1→4)Glc</td>
</tr>
</tbody>
</table>
Substitution of these core structures gives rise to lacto-, lactono-, muco-, gala-, globo- and globoiso-series glycosphingolipids with a large degree of variation in the non-core portion of the oligosaccharide structures. In recent years a great deal of research has been directed toward better understanding of the biological roles these naturally occurring compounds play, giving rise to the field of glycobiology. As a result, glycosphingolipids have been found to play important roles in a host of biological functions. As will be discussed next, glycosphingolipids have been shown to be involved in such processes as cell growth and differentiation, cell-cell recognition and adhesion, oncogenesis, molecular recognition, and neuronal repair.

There are several lines of evidence that suggest that glycosphingolipids influence the regulation of cell growth and proliferation: (1) contact inhibition of cell growth accompanies changes in ganglioside synthesis in transformed cell systems in vitro (gangliosides are sialic acid-containing glycosphingolipids), (2) loss of contact induced glycosphingolipid synthesis is associated with loss of contact inhibition and (3) the addition of exogenous gangliosides stimulates cell growth. Exogenous gangliosides are known to insert into cell membranes. Thus, addition of exogenous gangliosides leads to elevated levels of membrane-bound gangliosides.

The role of gangliosides in promoting cell adhesion has been demonstrated by several workers. Cheresh and co-workers have shown that monoclonal antibodies specific for gangliosides block cell attachment to the cellular adhesion glycoprotein fibronectin. Yamada et al. have shown that ganglioside-deficient NCTC 2071A cells, which ordinarily synthesize very little fibronectin and lack the ability to retain it at the cell surface as well as the ability to organize it into an extracellular fibrillar matrix, begin to retain and organize their fibronectin when cultured in
ganglioside-supplemented medium.\textsuperscript{64e} Yamada et al. have reported the rapid and specific adhesion of embryonic chick neural retina cells on plastic surfaces to which gangliosides were adsorbed but not on surfaces to which neutral glycosphingolipids or sulfatides were adsorbed.\textsuperscript{64a}

A great deal of data exist which demonstrate the involvement of glycosphingolipids in oncogenesis.\textsuperscript{65} The dramatic changes in glycosphingolipid composition and metabolism associated with oncogenic transformation are of two general types: (1) deletion of complex glycosphingolipids due to a block in synthesis together with a concomitant build-up of precursors and (2) synthesis of new glycosphingolipids due to activation of normally unexpressed glycosyltransferases.\textsuperscript{62a} Globotriaosylceramide (Gb\textsubscript{3}) is an important example of the glycosphingolipid class of marker molecules highly expressed in most Burkitt lymphoma cell lines (Scheme 4.2).\textsuperscript{65a}

Scheme 4.2
Ganglioside GD₃ is another well known tumor-associated antigen. GD₃ is expressed in human melanomas (Scheme 4.3).⁶⁵ᵇ,c Gu et al. have shown a direct relationship between the expression of GD₃ and the activity of GD₃ synthetase in liver cancer cells.⁶⁶ᵃ Glycosphingolipids carrying the Lewis Antigen X (Le⁺) determinant [Gal-β→4-(Fuc-α-1→3)-GlcNAc] accumulate in a number of human cancers.⁶⁵ᵈ-¹ Eto and Shinoda have analyzed the composition of gangliosides and neutral glycosphingolipids in various neural tumors, and have found abnormal ganglioside and neutral glycosphingolipid compositions associated with malignant transformation.⁶⁶ᵇ Kostic and Buchiet have found abnormal ganglioside compositions in gliomas that correlate with the degree of malignancy.⁶⁶ᶜ

Glycosphingolipids are known to act as receptors for a variety of bacterial toxins, peptide hormones and viruses.⁵⁰,⁶⁷ For example, gangliosides have been shown to act as membrane receptors for tetanus toxin⁶⁷ᵇ-e and cholera toxin.⁶⁷ᵃ,b,f,g In their landmark study, Holmgren et al. showed cholera toxin to be bound specifically only to
ganglioside GM₁ (Scheme 4.4). The amount of GM₁ and the binding ability for cholera toxin showed a direct relationship in human, porcine, and bovine intestinal mucosa.

Scheme 4.4

Markwell and colleagues have shown that some gangliosides function as receptors for Sendai virus. Treatment of virus-sensitive cells with sialidase (the enzyme which hydrolyzes gangliosides) rendered the cells resistant to the virus. Further treatment with purified gangliosides restores their sensitivity. Gangliosides have also been implicated as receptors for influenza viruses. Recently F. Gonzalez-Scarano et al. have demonstrated that galactosylceramide (GalC) acts as a receptor for HIV-1. When CD-4 negative cells were treated with antisera raised against GalC, subsequent infection with HIV-1 was inhibited. In addition, recombinant HIV surface glycoprotein gp 120 bound to GalC but not to other glycolipids.

In 1969 Wooley and Gommi demonstrated that sialidase destroys the serotonin response of rat stomach strips while brain ganglioside restores it. Berry-Kravis and Dawson showed that NCB-20 cells, which lack the more complex gangliosides found in brain and have only low affinity serotonin binding sites, exhibited a 10-fold
increase in serotonin receptor affinity upon exposure to exogenous gangliosides. Experiments on the binding of L-glutamate to receptors on rat brain synaptic plasma membranes show a marked stimulation of specific glutamate receptor binding by various gangliosides. It was shown that stimulation is due to an increased number of binding sites induced by ganglioside treatment rather than a change in receptor affinity.

Of great pharmacological interest is the fact that treatment of damaged neurons with various gangliosides often leads to neuronal repair. Karpia et al. have reported an acute effect associated with ganglioside treatment of CNS injuries. The ganglioside treatment resulted in reduced behavioral impairment (24 - 48 h after the injury) followed by long-term improved recovery. Several groups have found that ganglioside GM₁ stimulates the recovery of noradrenergic, dopaminergic, serotonergic and cholinergic neurons in brain after surgical and neurotoxin lesions. Preliminary clinical studies show that GM₁ has a favorable effect on the recovery of patients following ischemia or cerebral hemorrhage. GM₁ has been shown to restore the dopamine content in the striatum of mice afflicted with experimentally induced Parkinsonism. This effect is both dose and time dependent. Recently J. S. Schneider et al. reported the results of a similar GM₁ study involving primates. Their study reports that Parkinsonian-like symptoms were ameliorated after treatment with GM₁. In addition, treatment with GM₁ increased striatal dopamine and enhanced the dopaminergic innervation of the striatum.

In spite of the wide range of biological functions exhibited by glycosphingolipids, they are actually relatively scarce and only difficultly obtained in homogenous form from biological materials. In order to further explore their functions in biological systems, the synthesis of isomerically pure glycosphingolipids and analogs is necessary.
4.2 Hydrogen-Bonding Patterns in Glycosyl Acceptors

There are many approaches to the stereoselective synthesis of glycosphingolipids. The synthesis of glycosphingolipids has recently been reviewed. Two of the approaches which have been commonly used are shown in Scheme 4.5.

Scheme 4.5

These syntheses utilize either N-acyl-protected sphingosine derivatives or 2-azido-sphingosines as glycosyl acceptors. The yields for the latter case are usually quite good, while those for the former are usually poorer. Because of the poor reactivity exhibited by the N-acyl-protected glycosyl acceptors, harsh reaction conditions (reflux) are often required to effect bond formation. As a result, chemical yields suffer as well as the α- vs β-selectivity.
A similar trend in the reactivity of glycosyl acceptors used for O-linked glycopeptide synthesis has been reported. A likely explanation for this trend is the existence of different hydrogen-bonding patterns in the various glycosyl acceptors (Scheme 4.6). In the favorable hydrogen-bonding pattern, the nucleophilicity of the hydroxyl is enhanced relative to that involved in the unfavorable case. Polt and Szabo et al. have reported a mild and stereoselective glycosylation of N-diphenylmethylene-protected serine esters which capitalizes on the enhanced hydroxyl nucleophilicity imparted by the N-diphenylmethylene protecting group (Scheme 4.7).
Polt's method utilizes AgOTf as glycosylation catalyst. Chemical yields are excellent (81 - 90%) and the β-glycosides are formed stereospecifically. The success of this method suggested that derivatives of the N-diphenylmethylene-protected sphingosines described in Chapter 1 would also undergo favorable hydrogen-bonding and thus be ideal substrates for AgOTf catalyzed synthesis of glycosphingolipids (Scheme 4.8).
4.3 Stereoselective Synthesis of 1' and 3' β-Glycosyl-Threeo-Ceramides

Before the chemistry outlined in Scheme 4.8 could be attempted, it was necessary to synthesize an appropriately protected glycosyl acceptor. The first step in this process required protection of the C-3 hydroxyl (Scheme 4.9). Unfortunately, 32a and 32b proved unsatisfactory for the desired glycosyl acceptor synthesis as removal of the silyl ether protecting group using TBAF resulted in migration of the 3-O-benzoate to the 1-O position (Scheme 4.10).

\[ \text{Scheme 4.9} \]

\[ \text{Scheme 4.10} \]
Benzoyl migration was detected by resilylating compound 33a (Scheme 4.10). Comparison of the $^{13}$C, $^1$H, and IR spectra of 32a and 34 showed that they were clearly distinct compounds. In addition, the $^1$H and $^{13}$C NMR spectra for 34 were consistent with migration. Migration could be avoided by substituting the bulkier pivalate for the 3-O-benzoyl protection (Scheme 4.11). When 36b was resilylated, the product was identical (by NMR) to 35b, thus no migration had occurred (Scheme 4.11).

![Scheme 4.11]

When compounds 36a and 36b were treated with various glycosyl donors using the
method of Polt et al., the corresponding 1'-β-glycosphingolipids (37a-c) were obtained (Scheme 4.12).

\[
\begin{align*}
\text{R}^\prime & \text{O-}:\text{O} \quad + \quad \text{R}^\prime \text{O-}:\text{O} \\
36 & \text{R} \quad \text{AgOTf} \quad \text{CH}_2\text{Cl}_2 \\
37 & \text{R} \quad \text{AcO} \\
38 & \text{R'} \text{N}=\text{CPh}_2 \quad \text{BzO} \quad \text{AgOTf} \quad \text{CH}_2\text{Cl}_2
\end{align*}
\]

<table>
<thead>
<tr>
<th>St. Mat.</th>
<th>R</th>
<th>R'</th>
<th>R''</th>
<th>Glycosylation Product / Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>36a</td>
<td>\text{C}<em>{13}\text{H}</em>{27}</td>
<td>\text{CH}_2\text{OAc}</td>
<td>(\text{OAc})_4-\text{β-Gal}</td>
<td>37a 72%</td>
</tr>
<tr>
<td>36b</td>
<td>\text{C}<em>6\text{H}</em>{17}</td>
<td>\text{CH}_2\text{OAc}</td>
<td>(\text{OAc})_4-\text{β-Gal}</td>
<td>37b 71%</td>
</tr>
<tr>
<td>36b</td>
<td>\text{C}<em>6\text{H}</em>{17}</td>
<td>\text{CH}_2\text{OAc}</td>
<td>\text{Ac}</td>
<td>37c 69%</td>
</tr>
<tr>
<td>33a</td>
<td>\text{C}<em>6\text{H}</em>{17}</td>
<td>\text{H}</td>
<td>\text{Ac}</td>
<td>38a 56%</td>
</tr>
<tr>
<td>33a</td>
<td>\text{C}<em>6\text{H}</em>{17}</td>
<td>\text{CH}_2\text{OAc}</td>
<td>\text{Ac}</td>
<td>38b 63%</td>
</tr>
<tr>
<td>33a</td>
<td>\text{C}<em>6\text{H}</em>{17}</td>
<td>\text{CH}_2\text{OAc}</td>
<td>(\text{OAc})_4-\text{β-Gal}</td>
<td>38c 71%</td>
</tr>
<tr>
<td>33b</td>
<td>\text{C}_4\text{H}_9</td>
<td>\text{CH}_2\text{OAc}</td>
<td>(\text{OAc})_4-\text{β-Gal}</td>
<td>38d 60%</td>
</tr>
</tbody>
</table>

Scheme 4.12

The chemical yields for 37a-c were good (approximately 70%) and the
stereoselectivity was excellent (the α-anomers could not be detected by either $^1$H or $^{13}$C NMR). Compounds 33a and 33b could also be glycosylated using this methodology (Scheme 4.12). These compounds represent novel positional analogs of glycosphingolipids. The chemical yields for 38a-d were lower than those for 37a-c presumably due to steric factors. (One would expect the 2° glycosyl acceptors, 33, to be less reactive than 1° acceptors, 36, due to unfavorable steric interactions in the transition state leading to product).

1'β-Lactosyl-threo-ceramides were obtained from 37a and 37b via a three-step procedure: (1) TFA-catalyzed cleavage of the Schiff base, (2) N-acylation of the resulting amine with palmityl chloride and (3) saponification of the pivalate and acetate protecting groups with anhydrous NaOMe/MeOH (Scheme 4.13).
When \( n = 10 \), the product from the chemistry shown in scheme 4.13 is \( \beta \)-lactosyl-threo-ceramide. \( \beta \)-Lactosyl-erythro-ceramide is an important intermediate in the biosynthesis of more complex glycosphingolipids (Table 7). \( \beta \)-Lactosyl-erythro-ceramide is the substrate for biosynthetic formation of lacto-, lactoneo-, muco-, globo-, globoiso- and ganglio-series glycosphingolipids.\(^{74a,b}\) Since lactose is the basic unit of mammalian glycosphingolipids, a great deal of research has been devoted to providing suitably protected derivatives for further elaboration into more complex oligosaccharides.\(^{74c}\) Since \( \beta \)-lactosyl-erythro-ceramide is the naturally occurring isomer, the majority of lactosylceramides synthesized to date have had the erythro configuration. To the author's knowledge, the work presented in this chapter represents the first synthesis of \( \beta \)-lactosyl-threo-ceramide. The next section will outline the biological relevance of this threo isomer of the glycosphingolipid-parent, lactosylceramide.
4.4 Pharmacological Significance of *Threo*-Glycosphingolipids

As mentioned briefly in Chapter 1, *threo*-sphingosines and ceramides are of interest as pharmacologic agents due to their unique biological activities relative to the *erythro* isomers. Of particular note is the glucosyltransferase inhibitory activity of D-*threo*-2-decanoylamino-3-morpholino-1-phenyl-1-propanol (*threo*-PDMP) (Scheme 4.14).

![Scheme 4.14](image)

**D-** *threo*-2-decanoylamino-3-morpholino-1-phenyl-1-propanol

(*threo*-PDMP)

Studies of *threo*-PDMP *in vitro* show that it is a potent glucosyltransferase inhibitor. (Glucosyltransferase is the enzyme that couples ceramide to glucose. It is a member of a family of enzymes known as glycosyltransferases. Glycosyltransferases are enzymes that catalyze the transfer of glycosyl residues from a donor to an acceptor substrate). The *erythro* isomer was not active as an inhibitor. *Threo*-PDMP has been shown to cause a marked decrease in cellular glycosphingolipids in a variety of *in vitro* systems. For example, when B16 melanoma cells were incubated with...
threo-PDMP considerable decreases in glucosylceramide and lactosylceramide were reported.32g The treated cells were unable to bind to laminin or type IV collagen.32g When glucosylceramide was included in the incubation mixture, the effect of the inhibitor was counteracted. Threo-PDMP caused growth inhibition of cultured rabbit skin fibroblasts and a decrease in gangliosides GM₃ and GD₃.32k Metabolic labeling with [¹⁴C]-galactose showed reduced incorporation of radioactivity into gangliosides and glycosphingolipids when threo-PDMP was present. When BALB/c 3T3 cells were grown in the presence of threo-PDMP, a substantial decrease in the level of all glycosphingolipids and an accumulation of ceramide were noted.32f Cell growth inhibition of neuroblastoma cells caused by threo-PDMP has recently been reported.32m Metabolic labeling with [¹⁴C]-galactose showed decreased incorporation of the radio label in gangliosides and glycosphingolipids when threo-PDMP was in the medium.32m Threo-PDMP has also been shown to block the adherence of HL-60 during phorbol ester-induced macrophage differentiation. Inhibition of glycosphingolipid synthesis correlated with inhibition of adherence but not macrophage differentiation.32l

The mechanism of action for threo-PDMP is presently unknown. At first glance it seems reasonable to assume that the morpholine moiety of threo-PDMP is recognized by the glucose-binding portion of the enzyme while the ceramide moiety is recognized by the portion that binds to ceramide. Preferential binding of this transition-state mimic would inhibit the enzyme from reacting with its true substrates. Vannum and Radin have suggested that there are four recognition sites within the active site of the enzyme: (1) an anionic moiety that may bind the glucose in activated form, (2) an oxygen-binding region oriented toward the third carbon atom of ceramide, (3) a narrow region that binds the alkyl chain of the fatty acid moiety and (4) a less narrow region that binds the hydrocarbon chain of the sphingosine (Scheme 4.15).32d
That erythro-PDMP did not act as an inhibitor gives rise to the idea that the 3-OH of erythro-ceramide may cause the enzyme to adopt a catalytically active form after binding to the glycosyltransferase. This conclusion was consistent with kinetic data.
obtained by Radin and Inokuchi.\textsuperscript{32e} That \textit{erythro}-PDMP is not active as an inhibitor, coupled with the fact that several \textit{threo}-ceramide analogs which lack the 3-morpholino substituent are active as inhibitors (Scheme 4.16), suggests that the key to enzyme inhibition lies in the \textit{threo} \(\beta\)-amino alcohol moiety and not in the 3-morpholino substituent!

\begin{center}
\includegraphics[width=\textwidth]{Scheme_4.16.png}
\end{center}

\textbf{Scheme 4.16}

Although it has long been known that changes in cell surface glycosphingolipids accompany malignancy,\textsuperscript{65} it is only recently that these changes have been shown to correlate with altered glycosyltransferase expression.\textsuperscript{76} Several authors have reported that elevations of serum glycosyltransferases correlate with the presence of malignancy in humans.\textsuperscript{77} Interest in \textit{threo}-PDMP and other glycosyltransferase inhibitors has increased as these correlations have become apparent.\textsuperscript{78} It has been suggested that specific inhibitors of these glycosyltransferases may potentially be used as cancer chemotherapeutic agents.\textsuperscript{78}

The search for effective glycosyltransferase inhibitors is at an early stage.\textsuperscript{78} Since little is known about the functional groups in the active sites of these enzymes, designing efficient inhibitors must be done empirically.\textsuperscript{32d} In addition to \textit{threo}-PDMP, other glycosyltransferase inhibitors have been synthesized (Scheme 4.17).
The inhibitors shown in Scheme 4.17 fall into two general categories: (1) sugar nucleotide analogs in which a P-O bond has been replaced with a P-C bond and (2) specific acceptor substrate analogs in which the active hydroxyl has been chemically masked \((R \neq \text{OH})\). All of these inhibitors have been tested \textit{in vitro} and exhibit competitive inhibition.\textsuperscript{79}
The potential of compounds 41a and 41b to act as glycosyltransferase inhibitors should be obvious (Scheme 4.13). Their possession of the lactose moiety should allow them to bind to glycosyltransferases involved in the biosynthesis of lacto-, lactoneo-, muco-, globo-, globoiso-, and ganglio-series glycosphingolipids. (All of these series are based on lactose as the first unit of their core structure). Their possession of the threo-ceramide moiety should render them effective inhibitors via a mechanism similar to that involved with threo-PDMP. Although the structural similarity between compounds 38a-d and threo-PDMP is slim, deprotected 38a-d may inhibit glycosyltransferases via an entirely different mechanism.

At the time of this writing, compounds 41a and 41b are being tested for their effect on in vitro glycosphingolipid synthesis and tumor cell invasiveness using the protocol developed by Hendrix et al. at the University of Arizona College of Medicine. Hendrix et al. recently showed that swainsonine and deoxynorjirimycin, both \( \alpha \)-mannosidase inhibitors, decreased the ability of an invasive human melanoma cell line to invade a reconstituted basement membrane in vitro. This decrease in invasive ability correlated with changes in the cell surface oligosaccharides.
4.5 Conclusion

A series of N-diphenylmethylene-protected glycosyl acceptors was synthesized. These glycosyl acceptors were shown to undergo β-specific glycosylation using the method of Polt et al.\textsuperscript{73} This method capitalizes on the favorable hydrogen-bonding pattern imparted by the N-diphenylmethylene protection. This favorable hydrogen-bonding enhances the nucleophilicity of the glycosyl acceptor relative to glycosyl acceptors with more conventional N-protection (\textit{i.e.} Cbz, Boc, acyl \textit{etc.}). This enhanced nucleophilicity allows the glycosylation to be carried out under mild conditions (AgOTf, CH\textsubscript{2}Cl\textsubscript{2}, RT overnight) and provides the corresponding glycosphingolipids in good chemical yield (approximately 70%).

Cleavage of the N-diphenylmethylene protecting group from the glycosphingolipids synthesized via this method could be accomplished selectively without cleaving the glycosidic bond or the carbohydrate acetate protection. N-Acylation with palmityl chloride, followed by NaOMe/MeOH deacetylation, provided two β-lactosylceramide analogs. These analogs possess the unnatural \textit{threo}-configuration in the ceramide moiety. This configuration may render them active as glycosyltransferase inhibitors. Studies are presently underway at the University of Arizona College of Medicine to determine their effect on synthesis of glycosphingolipids and invasion of basement membranes by human melanoma cell lines.
CHAPTER 5

EXPERIMENTAL
5.1 Synthesis of Benzophenone Schiff Base Esters (1a-i)

**Ethyl N-(Diphenylmethylene)-L-alaninate (1a):**

Diphenylketimine (9.88 g, 54.6 mmol) was added to a stirred solution of L-alanine ethyl ester hydrochloride (10.1 g, 66.0 mmol) in CH$_2$Cl$_2$ (100 mL). The resulting mixture was stirred overnight under argon. Crude product was isolated by washing the organic layer with 1% NaHCO$_3$, saturated NaHCO$_3$ (2 X), and brine. After drying over K$_2$CO$_3$ the CH$_2$Cl$_2$ layer was evaporated under reduced pressure. Pure product was obtained as a white solid (12.97 g, 46.2 mmol, 85%) after recrystallizing from 10% EtOAc in hexanes.

$^1$H NMR (CDCl$_3$): δ 7.7 - 7.6 (m, 2 H), 7.5 - 7.3 (m, 6 H), 7.25 - 7.15 (m, 2 H), 4.23 - 4.10 (m, 3 H), 1.43 (d, 3 H, J = 6.7 Hz), 1.25 (t, 3 H, J = 7 Hz); $^{13}$C NMR (CDCl$_3$): δ 172.46, 169.25, 139.20, 136.00, 129.96, 128.44, 128.30, 127.73, 127.35, 60.45, 60.33, 18.87, 13.90; IR (KBr): 1736.3, 1624.8, 1449.5, 1375.9, 1285.0, 1196.9, 1127.6, 787.1, 704.2; [α]$_D$ = -90.0° (c = 2, CHCl$_3$); m.p. = 52 - 53 °C.

**Methyl N-(Diphenylmethylene)-L-phenylalaninate (1b):**

Diphenylketimine (3.96 g, 21.9 mmol) and L-phenylalanine methyl ester hydrochloride (5.20 g, 24.2 mmol) were stirred in approximately 50 mL of CH$_2$Cl$_2$ at RT overnight. The organic layer was washed with 1% NaHCO$_3$, saturated NaHCO$_3$ (2 X) and dried over K$_2$CO$_3$. The solvent was evaporated under reduced pressure. Pure product was obtained after recrystallizing from 5% EtOAc in hexanes (5.7 g, 16.6 mmol, 76%).

$^1$H NMR (CDCl$_3$): δ 7.60 - 7.55 (m, 2 H), 7.36 - 7.14 (m, 9 H), 7.04 - 7.00 (m, 2 H), 6.58 (d, 2 H, J = 6 Hz), 4.26 (dd, 1 H, J = 4.3, 9.3 Hz), 3.72 (s, 3 H), 3.28 (dd, 1 H, J = 4.3, 13.2 Hz), 3.17 (dd, 1 H, J = 9.3, 13.2 Hz); $^{13}$C NMR (CDCl$_3$): δ
Methyl N-(Diphenylmethylene)-serinate (1c):

L-Serine methyl ester hydrochloride (3.52 g, 22.7 mmol) was added to a solution of diphenylketimine (3.72 g, 20.6 mmol) in CH₂Cl₂ (30 mL) and the resulting mixture stirred at RT. After 48 h the solution was poured onto 1% NaHCO₃ (30 mL). The organic layer was separated and washed with saturated NaHCO₃ (2 X 30 mL), dried over MgSO₄ and evaporated under reduced pressure. Crude product was recrystallized to afford 5.18 g of white crystalline product (18.3 mmol, 89%).

$^1$H NMR (CDCl₃): δ 7.7 - 7.65 (m, 2 H), 7.55 - 7.50 (m, 2 H), 7.4 - 7.2 (m, 6 H), 4.25 (t, 0.3 H, J = 5.1 Hz), 4.0 - 3.93 (m, 2.6 H), 3.76 (s, 2 H), 3.72 (s, 1 H), 3.14 - 3.10 (bs, 0.7 H), 2.57 (dd, 0.3 H, J = 5.8, 7.7 Hz); $^1$H NMR (d₆-benzene): δ 7.84 - 7.80 (m, 1.9 H), 7.72 (m, 1.1 H), 7.20 - 6.98 (m, 7 H), 4.34 (t, 0.5 H, J = 5.3 Hz), 4.05 (d, 0.9 H, J = 5.2 Hz), 3.83 - 3.70 (m, 1.6 H), 3.26 (s, 1.3 H), 3.16 (s, 1.7 H), 2.6 (bs, 0.5 H); $^{13}$C NMR (CDCl₃): δ 172.57, 142.78, 142.54, 130.60, 128.78, 128.53, 128.13, 127.98, 127.78, 127.60, 126.51, 125.57, 101.07, 67.29, 66.46, 64.15, 59.56, 52.41, 52.12; Note: OCH₂, NCH, OCH₃ resonances appear twice due to imine oxazolidine tautomerism; IR (KBr): 3500 - 3300, 1736.4, 1446.6, 1338.5, 1228.4, 750.9, 703.7, 630.6 cm⁻¹; MS (EI): 283 (M⁺), 224 (M-CO₂Me), 206 (M - H₂O - CO₂Me, bp); [α]D = - 136.14 ° (c = 8.5, CHCl₃), Anal. Calc. for C₇₂.07 H₆.05 N₄.94; found: C₇₁.78, H₅.94, N₄.96.
**Methyl O-(tert-Butyldimethylsilyl)-N-(diphenylmethylene)-L-serinate (1d):**

To a stirred solution of methyl N-(diphenylmethylene)-L-serinate (3.20 g, 11.3 mmol) in dry DMF (10 mL) was added imidazole (1.97 g, 29.0 mmol) and TBDMSCl (2.76 g, 18.3 mmol). The mixture was stirred under argon for 24 h. After 24 h the reaction mixture was poured onto diethyl ether, extracted with 1% NaHCO₃ (2 x 15 mL) and washed with brine. The organic layer was dried over MgSO₄ and the solvent removed under reduced pressure. Crude product was recrystallized from 5% EtOAc in hexanes to yield 4.10 g of white crystals (10.34 mmol, 92%).

$^1$H NMR (CDCl₃): δ 7.6 - 7.5 (m, 2 H), 7.5 - 7.2 (m, 8 H), 4.30 (dd, 1 H, J = 5.4, 7.6 Hz), 4.11 (dd, 1 H, J = 5.4, 9.8 Hz), 3.92 (dd, 1 H, J = 7.6, 9.8 Hz), 3.68 (s, 3 H), 0.82 (s, 9 H), 0.00 (s, 3 H), -0.023 (s, 3 H); $^{13}$C NMR (CDCl₃): δ 171.28, 170.75, 139.25, 135.94, 130.08, 128.64, 128.41, 128.86, 128.17, 127.91, 67.48, 64.43, 51.63, 25.61, 18.02, -5.51, -5.62; IR (Neat): 1725.2, 1625.1, 1285.6, 1125.3, 1074.6, 829.9, 779.2, 686.4 cm⁻¹; MS (EI): 397 (M⁺), 340 (M-tBu, bp); [α]D = -95.1 ° (c = 3.6, CHCl₃); m.p. = 57 - 59 °C.

**Ethyl N-(Diphenylmethylene)-glycinate (1e):**

See references 16 and 17.

**Methyl N-(Diphenylmethylene)-L-alaninate (1f):**

L-Alanine methyl ester hydrochloride (4.33 g, 31.1 mmol) and diphenylketimine (5.10 g, 28.2 mmol) were stirred in approximately 80 mL of CH₂Cl₂ under argon at room temperature for 24 h. The reaction mixture was poured onto 1% NaHCO₃, separated, and washed with two volumes of saturated NaHCO₃. The organic layer was then dried over K₂CO₃, filtered, and removed under reduced pressure. Pure product was obtained after flash chromatography using 40% EtOAc in hexanes as eluent (6.62 g, 25 mmol, 80%).
\( ^1 \)H NMR (CDCl\(_3\)): \( \delta \) 7.70 - 7.65 (m, 2 H), 7.5 - 7.25 (m, 6 H), 7.23 - 7.15 (m, 2 H), 4.18 (q, 1 H, \( J = 6.7 \) Hz), 3.71 (s, 3 H), 1.42 (d, 3 H, \( J = 6.7 \) Hz); \( ^{13} \)C NMR (CDCl\(_3\)): \( \delta \) 173.13, 169.48, 139.22, 135.96, 130.11, 128.55, 128.46, 128.40, 127.84, 127.43, 60.36, 51.86, 19.00; IR (KBr): 1748.7, 1629.0, 1448.2, 1448.0, 1368.2, 1281.4, 1071.6, 712.0; \([\alpha]_D = -105.4^\circ\) (c = 3.25, CHCl\(_3\)); m.p. = 69 - 72 °C.

**Benzyl N-(Diphenylmethylene)-L-alaninate (1g):**

Diphenylketimine (1.98 g, 10.9 mmol) was added to a stirred solution of L-alanine benzyl ester hydrotosylate\(^{81}\) (4.5 g, 12.8 mmol) in CH\(_2\)Cl\(_2\) (50 mL) and stirred for 28 h at room temperature under argon. The mixture was then washed with 0.1% NaHCO\(_3\), saturated NaHCO\(_3\) (2 X) and brine, then dried over K\(_2\)CO\(_3\). The solvent was removed under reduced pressure and the resulting oil chromatographed using 10% EtOAc in petroleum ether as eluent. Pure product was obtained as a colorless oil (3.0 g, 8.7 mmol, 80%).

\( ^1 \)H NMR (CDCl\(_3\)): \( \delta \) 7.7 - 7.6 (m, 2 H), 7.4 - 7.25 (m, 11 H), 7.2 - 7.1 (m, 2 H), 5.19 (d, 1 H, \( J = 12.5 \) Hz), 5.12 (d, 1 H, \( J = 12.5 \) Hz), 4.21 (q, 1 H, \( J = 6.7 \) Hz), 1.45 (d, 3 H, \( J = 6.7 \) Hz); \( ^{13} \)C NMR (CDCl\(_3\)): \( \delta \) 172.49, 169.78, 139.32, 136.08, 135.88, 130.20, 128.64, 128.48, 128.34, 127.95, 127.81, 127.52, 66.27, 60.53, 19.01; IR (Neat): 1919.2, 1736.9, 1619.3, 1490.1, 1448.9, 1178.6 cm\(^{-1}\); \([\alpha]_D = -65.7^\circ\) (c = 1.3, CHCl\(_3\)).

**Benzhydryl N-(Diphenylmethylene)-L-alaninate (1h):**

A solution of L-alanine benzhydryl ester hydrotosylate\(^{82}\) (3.0 g, 7.1 mmol) and diphenylketimine (1.2 g, 6.6 mmol) in 30 mL CH\(_2\)Cl\(_2\) was stirred at RT. After 24 h the reaction mixture was poured onto 0.1% NaHCO\(_3\), washed with saturated NaHCO\(_3\) (2 X) and dried over K\(_2\)CO\(_3\). The solvent was removed under reduced pressure and the
crude product chromatographed using 20% EtOAc in petroleum ether. Pure product was obtained as a white solid in 81% yield (2.1 g, 5.3 mmol).

$^1$H NMR (CDCl$_3$): $\delta$ 7.7 - 7.6 (m, 2 H), 7.45 - 7.25 (m, 16 H), 7.2 - 7.1 (m, 2 H), 6.89 (s, 1 H), 4.25 (q, 1 H, $J = 6.7$ Hz), 1.48 (d, 3 H, $J = 6.7$ Hz); $^{13}$C NMR (CDCl$_3$): $\delta$ 171.14, 169.52, 139.85, 139.06, 135.82, 130.05, 128.45, 128.27, 128.11, 127.74, 127.59, 127.44, 127.27, 126.88, 126.56, 76.64, 60.64, 18.61; IR (KBr): 3060.3, 2931.0, 2355.1, 1736.9, 1625.2, 1495.9, 1448.9, 1372.5, 1178.6, 1119.9 cm$^{-1}$; $[\alpha]_D = -46.5^\circ$ (c = 2.2, CHCl$_3$); m.p. = 82 - 85 °C.

tert-Butyl N-(diphenylmethylene)-L-alaninate (1i):

Diphenylketimine (1.8 g, 9.9 mmol) was added to a stirred solution of L-alanine tertbutyl ester hydrochloride (2 g, 11.1 mmol) in CH$_2$Cl$_2$ (20 mL) and the resulting mixture stirred overnight under argon. Crude product was isolated by extracting the organic layer with 1% NaHCO$_3$, saturated NaHCO$_3$ (2 X) and washing with brine. The organic layer was dried over K$_2$CO$_3$ and evaporated under reduced pressure. Pure product was obtained as a white solid (2.45 g, 7.9 mmol, 80%) after recrystallization (EtOAc in hexanes).

$^1$H NMR (CDCl$_3$): $\delta$ 7.7 - 7.6 (m, 2 H), 7.5 - 7.25 (m, 6 H), 7.22 - 7.15 (m, 2 H), 4.03 (q, 1H, $J = 6.7$ Hz), 1.44 (s, 9 H), 1.40 (d, 3 H, $J = 6.7$ Hz); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 171.77, 169.07 (quaternary, ester and imine), 139.49, 136.35 (quaternary, aromatic), 132.23, 129.96, 129.82, 128.52, 128.32, 128.08, 127.81, 127.49 (CH, aromatic), 80.47 (quaternary, tBu), 61.06 (CHN), 27.86, 18.98 (CH$_3$); $[\alpha]_D = -52.6^\circ$ (c = 1.2, CHCl$_3$).
5.2 Compounds Demonstrating Reactivity of the Schiff Base (2a-d)

(2S)-2-[N-(Diphenylmethylene)amino]-1,1-diphenyl-propan-1-ol (2a):
A flame dried reaction vessel was charged with 286 mg methyl N-(diphenylmethylene)-L-alaninate (1.02 mmol) and 5 mL of dry CH₂Cl₂. The solution was then chilled to -78 °C in a dry ice acetone bath. When the solution had chilled for approximately 15 minutes, 1 mL of 3 M PhMgBr in Et₂O (3 mmol) was added. The resulting mixture was stirred for approximately 10 min at -78 °C then warmed to RT and allowed to stand an additional 45 min. The mixture was then poured onto saturated NaHCO₃ and the product extracted with 2 volumes of CH₂Cl₂. The combined CH₂Cl₂ layers were dried over K₂CO₃ and then removed by rotary evaporation. Pure product was isolated in 95% yield after flash chromatography (371 mg, 0.95 mmol).

\(^1\)H NMR (CDCl₃): \(\delta\) 7.55 - 7.0 (m, 20 H), 4.78 (s, 1 H), 4.39 (q, 1 H, J = 6.3 Hz), 1.13 (d, 3 H, J = 6.3 Hz); \(^1^3\)C NMR APT (CDCl₃): \(\delta\) 167.27 (quaternary, imine), 147.60, 144.32, 139.61, 136.69 (quaternary, aromatic), 130.08, 128.73, 128.32, 127.93, 127.82, 127.70, 127.64, 126.34, 126.23, 125.95, 125.67 (CH, aromatic), 79.47 (quaternary), 63.59 (CHN), 17.33 (CH₃); IR (Neat): 3656.4 - 3133.6 (OH), 3063.0, 1627.2, 1577.7, 1493.0, 1443.5, 1365.8, 1316.3, 1281.0, 1182.1, 1069.1, 1033.7, 998.4, 744.1, 1694.6, 645.2 cm⁻¹ \([\alpha]_D = +36.0^\circ\) (c = 0.76, CHCl₃); MS (CI-Methane): M + 1 = 392, (M + 1)-C₆H₆ = 314.

(2S)-2-[N-(Diphenylmethylene)amino]-3-phenyl-propan-1-ol (2b):
To a stirred solution of methyl N-(diphenylmethylene)-L-phenylalaninate (350 mg, 1.02 mmol) in CH₂Cl₂ (10 mL) at -78 °C under argon was added 5.1 mL of 0.48 M DIBAL in CH₂Cl₂ (2.5 mmol, 2.5 eq). PhMgBr was then added (3 mmol) and the reaction allowed to stir at -78 °C for 10 h. The reaction was then warmed to RT and
allowed to stand for several hours before pouring onto NaHCO₃ (sat'd). The aqueous layer was extracted twice with equal volumes of CH₂Cl₂. The organic layers were combined and dried over K₂CO₃. Solvents were removed by rotary evaporation. Crude product was obtained in 91% yield as a yellowish solid (288 mg, 0.91 mmol). Pure product was obtained after recrystallizing from EtOAc and hexanes.

¹H NMR (CDCl₃): δ 7.55 - 7.47 (m, 2 H), 7.4 - 7.1 (m, 9 H), 7.0 - 6.9 (m, 2 H), 6.50 (d, 2H, J = 6.8 Hz), 3.9 - 3.8 (m, 1 H), 3.7 - 3.6 (m, 2 H), 3.2 - 3.0 (bs, 1 H), 2.82 (d, 2 H, J = 6.4 Hz); ¹³C NMR (CDCl₃): δ 169.90, 138.76, 136.58, 130.00, 129.70, 128.56, 128.09, 127.97, 127.67, 125.91, 70.35, 66.10, 65.48, 59.41, 39.60, 38.98; m. p. = 125 - 127 °C.

(2S)-2-[N-(Benzhydryl)amino]-propan-1-ol (2c):

A flame dried reaction vessel was charged with ethyl N-(diphenylmethylene)-L-alaninate (227 mg, 0.80 mmol) and 10 mL CH₂Cl₂. The solution was chilled to -78 °C under argon for approximately 20 min. Neat DIBAL (5.6 mmol, 7 eq) was then added. The reaction was allowed to stir an additional 15 min at -78 °C followed by several h at RT. The reaction was quenched by pouring onto saturated NaHCO₃ and the product extracted with several volumes of CH₂Cl₂. The combined organic layers were dried (K₂CO₃), filtered, and the solvents were removed under reduced pressure. The crude product was recrystallized from 10% EtOAc and hexanes to yield 130 mg pure product (0.54 mmol, 68%).

¹H NMR (CDCl₃): δ 7.4 - 7.1 (m, 10 H), 5.01 (s, 1 H), 3.56 (dd, 1 H, J = 4.2, 10.6 Hz), 3.27 (dd, 1 H, J = 7.2, 10.6 Hz), 2.84 - 2.72 (m, 1 H), 2.05 - 1.50 (bs, 2 H), 1.08 (d, 3 H, J = 6.5 Hz); ¹³C NMR (CDCl₃): δ 128.50, 128.09, 127.32, 127.06, 127.00, 65.98, 63.90, 51.64, 17.14; [α]D = + 31.2 ° (c = 0.48, CHCl₃).
(2S)-2-[N-(Benzhydryl)amino]-1,1-diphenyl-3-phenyl-propan-1-ol (2d):

To a stirred solution of methyl N-(diphenylmethylene)-L-phenylalaninate (110 mg, 0.32 mmol) in CH$_2$Cl$_2$ (8 mL) was added PhMgBr (1.2 mmol, 3.8 eq). The mixture was allowed to stir for 1.5 h at -78 °C, then warmed to RT for 2 h. The flask was chilled again to -78 °C and 2.2 mmol DIBAL (7 eq) was then added. The mixture was stirred for 15 min at -78 °C and then warmed to RT overnight. Crude product was isolated by pouring onto NaHCO$_3$ (sat'd) and extracting with several volumes of CH$_2$Cl$_2$. The combined organic layers were dried over K$_2$CO$_3$ and evaporated under reduced pressure to yield 149 mg crude product (0.30 mmol, 94%). Product was recrystallized in two crops from 10% EtOAc in hexanes (116 mg, 73%).

$^1$H NMR (CDCl$_3$): δ 7.75 - 7.60 (m, 4 H), 7.40 - 7.0 (m, 17 H), 6.85 - 6.75 (m, 2 H), 6.30 (d, 2 H, J = 7 Hz), 5.09 (s, 1 H), 3.96 (s, 1 H), 3.86 (dd, 1 H, J = 2.6, 10.4 Hz), 2.90 (dd, 1 H, J = 2.4, 14.3 Hz), 2.38 (dd, 1 H, J = 10.4, 14.3 Hz), 2.08 (s, 1 H); $^{13}$C NMR (CDCl$_3$): δ 147.71, 145.26, 143.44, 141.41, 139.03, 129.41, 128.65, 128.21, 128.12, 128.06, 128.00, 127.39, 127.12, 126.62, 126.44, 126.30, 125.80, 125.41, 76.42, 63.28, 62.53, 37.76; m. p. = 146 - 148 °C.
5.3 Synthesis of Norpseudoephedrines (3a-e):

Method A (2 eq DIBAL):

The Schiff base ester (1.0 mmol) was dissolved in 10 mL of dry CH₂Cl₂ and cooled to -78 °C under an argon atmosphere. Two equivalents of DIBAL were then added via gas-tight syringe (4.0 mL of 0.5 M DIBAL in hexanes) over 1.5 h. The reaction was stirred 15 min before three equivalents of PhMgBr (1.0 mL of 3 M PhMgBr in Et₂O) was added in one portion. The light yellow solution was stirred an additional 15 min at -78 °C. After stirring at room temperature for 3 h the reaction was quenched by pouring onto 15 mL of saturated NaHCO₃. An additional 20 mL of CH₂Cl₂ was used in several portions to ensure complete transfer. (Note: These exact proportions of CH₂Cl₂ : NaHCO₃ are recommended to avoid formation of intractable emulsions). The aqueous layer was extracted with two additional 20 mL portions of CH₂Cl₂. The combined organic layers were dried over K₂CO₃, then filtered through Celite and evaporated under reduced pressure. Product was purified via flash chromatography in all cases except N-(diphenylmethylene)-1-phenyl ethanolamine in which case product was purified by recrystallizing from CH₂Cl₂ or THF. Solvent systems used for chromatography and yields for the two methods are listed in parentheses.

Method B (DIBAL : TRIBAL):

A flame dried reaction vessel was charged with 1.0 mmol of Schiff base ester and 10 mL of freshly distilled CH₂Cl₂. After chilling at -78 °C under argon for approximately 30 min, 1.1 equivalent of DIBAL : Triisobutylaluminum (TRIBAL) (1:1) was added (2.2 mL of 0.5 M solution in hexanes) via syringe pump. Addition required approximately 15 min. After addition was complete, 3 equivalents of PhMgBr was added in one portion (1.0 mL of 3 M solution in Et₂O). The reaction was allowed to stir for 1 h at -78 °C followed by 1 h at room temperature. The reaction
was quenched by pouring onto 15 mL of saturated NaHCO₃. An additional 20 mL CH₂Cl₂ was used to ensure complete transfer (Note: These exact proportions of CH₂Cl₂ : NaHCO₃ are recommended to avoid formation of intractable emulsions). The aqueous layer was then extracted with two additional 20 mL portions of CH₂Cl₂. The combined organic layers were dried over K₂CO₃, filtered through Celite, then removed by rotary evaporation. Product was purified via flash chromatography in all cases except N-(diphenylmethylene)-1-phenyl ethanolamine in which case product was purified by recrystallizing from CH₂Cl₂ or THF. Solvent systems used for chromatography and yields for the two methods are listed in parentheses.

(1S,2S)-2-[N-(Diphenylmethylene)amino]-1-phenylpropan-1-ol (3a):
(Oil, 54% method A, 78% method B; chromatography eluent: 15 % EtOAc in petroleum ether).
\[ \text{\textsuperscript{1}H NMR (CDCl}_{3} ): \delta 7.8 - 7.75 (m, 2 H), 7.65 - 7.55 (m, 2 H), 7.4 - 7.1 (m, 11 H), 4.42 (d, 1 H, J = 8.5 Hz), 3.11 (dq, 1 H, J = 6.4, 8.5 Hz), 2.58 - 2.36 (bs, 1 H), 1.22 (d, 3 H, J = 6.4 Hz); \text{\textsuperscript{13}C NMR APT (CDCl}_{3} ): \delta 145.50, 139.71 (quaternary, aromatic), 128.26, 128.21, 128.09, 127.65, 127.44, 127.15, 126.71, 126.30, 125.38 (CH, aromatic), 99.91 (quaternary, oxazolidine), 88.57 (CHO), 62.99 (CHN), 15.58 (CH₃); IR (Neat): 1726.4, 1490.0, 1450.8, 1235.9, 749.7, 698.9, 630.4 cm\(^{-1}\); [\alpha]D = + 198.9° (c = 1, CHCl₃)."

(1R,2S)-2-[N-(Diphenylmethylene)amino]-1-phenylpropan-1-ol (3a"):
To a stirred solution of (1R,2S)-norephedrine hydrochloride (2.5 g, 13.3 mmol, 1.1 eq) in CH₂Cl₂ (50 mL) was added diphenylketimine (2.13 g, 11.8 mmol). The resulting solution was stirred overnight at RT under argon. The reaction mixture was
washed with 1% NaHCO₃ and NaHCO₃ (sat'd), then dried over K₂CO₃. Solvents were removed under reduced pressure to yield 3.34 g product as an oil (10.6 mmol, 90%).

**1H NMR** (CDCl₃): δ 7.8 - 7.70 (m, 15 H), 5.0 (d, 0.5 H, J = 7.8 Hz), 4.77 (d, 0.5 H, J = 4.7 Hz), 3.67 - 3.14 (m, 1 H), 3.15 (bs, 0.5 H), 2.35 - 2.55 (bs, 0.5 H), 1.03 (d, 1.5 H, J = 6.3 Hz), 0.73 (d, 1.5 H, 6.7 Hz); **13C NMR APT** (CDCl₃): δ 167.36 (quaternary, imine), 144.64, 144.16, 140.02, 136.66 (quaternary, aromatic), 130.02, 128.34, 128.26, 128.17, 128.02, 127.96, 127.87, 127.43, 127.34, 127.26, 127.19, 127.08, 126.55, 126.37, 126.15, 125.28 (CH, aromatic), 99.23 (quaternary, oxazolidine), 80.91, 77.03 (CHO), 63.21, 57.00 (CHN), 16.16, 15.81 (CH₃); IR (Neat): 1625.6, 1492.4, 1450.4, 747.7, 697.5 cm⁻¹; [α]D = - 8.6° (c = 1.4, CHCl₃).

**(1S,2S)-2-[N-(Diphenylmethylene)amino]-1,3-diphenyl-propan-1-ol** (3b):

(Oil, 69% method A, 75% method B; chromatography eluent: 10% EtOAc in petroleum ether).

**1H NMR** (CDCl₃): δ 7.8 - 7.0 (m, 20 H), 5.88 (d, 0.5 H, J = 7 Hz), 4.86 - 4.81 (bs, 0.25 H), 4.58 (d, 0.75 H, J = 8.2 Hz), 3.9 - 3.8 (bs, 0.25 H), 3.63 - 3.56 (dt, 0.3 H, J = 2.8, 6.9 Hz), 3.48 - 3.40 (m, 0.75 H), 3.0 (d, 0.5 H, J = 7 Hz), 2.87 (dd, 0.75 H, J = 4.2, 14.4 Hz), 2.72 (dd, 0.75 H, J = 8.8, 14.4 Hz); **13C NMR** (CDCl₃): δ 169.52, 145.33, 145.25, 143.19, 139.87, 138.99, 138.63, 138.20, 135.96, 130.05, 129.90, 129.81, 128.85, 128.26, 128.19, 128.08, 127.96, 127.64, 127.50, 127.43, 127.20, 127.14, 126.93, 126.82, 126.16, 126.12, 125.93, 125.84, 125.60, 99.94, 85.78, 75.80, 69.86, 67.98, 40.16, 37.21; (Note Schiff base-oxazolidine tautomerism); IR (Neat) : 1601.0, 1495.2, 1451.3, 1222.0, 1028.7, 953.7, 743.8, 701.0 cm⁻¹; [α]D = + 68.4° (c = 2.4, CHCl₃).
-silyl)-1-phenyl-propan-1,3-diol  (3d):

(Oil, 62% method A, 73% method B; chromatography eluent: 10% EtOAc in petroleum ether).

$^1$H NMR (CDCl$_3$): δ 7.9 - 7.75 (m, 2 H), 7.65 - 7.50 (m, 2 H), 7.45 - 7.15 (m, 11 H), 4.96 (d, 1 H, J = 8.4 Hz), 3.89 (dd, 1 H, J = 3.2, 10.8 Hz), 3.67 (dd, 1 H, J = 1.6, 10.8 Hz), 3.4 - 3.25 (bs, 1 H), 3.20 - 3.14 (m, 1 H), 0.88 (s, 9 H), 0.11 (s, 3 H), 0.07 (s, 3 H); $^{13}$C NMR APT (CDCl$_3$): δ 145.58, 145.34, 140.46 (quaternary, aromatic), 128.32, 128.11, 128.06, 127.55, 127.49, 127.26, 126.85, 126.64, 125.71, (CH, aromatic), 100.09 (quaternary, oxazolidine), 81.86 (CHO), 68.33 (CHN), 59.13 (CH$_2$O), 25.75 (CH$_3$, tBu), 18.10 (quaternary, tBu), -5.5 (SiCH$_3$); IR (Neat): 1662.2, 1600.5, 1490.4, 1450.0, 1253.7, 1089.6, 1065.1, 837.2, 777.6, 750.4, 699.2 cm$^{-1}$, [α]$_D$ = + 101.9° (c = 7.7, CHCl$_3$).

N-(Diphenylmethylene)-1-phenyl-ethanolamine  (3e):

(White solid, 64% method A, 86% method B).

$^1$H NMR (CDCl$_3$): δ 7.7 - 7.6 (m, 2 H), 7.5 - 7.2 (m, 11 H), 7.1 - 7.0 (m, 2 H), 4.96 (dd, 1 H, J = 3.8, 8.4 Hz), 3.72 (s, 1 H), 3.62 (dd, 1 H, J = 3.8, 14.4 Hz), 3.47 (dd, 1 H, J = 8.5, 14.4 Hz); $^{13}$C NMR APT (CDCl$_3$): δ 169.89 (quaternary, imine), 142.13, 139.17, 136.49 (quaternary, aromatic), 130.31, 128.55, 128.39, 128.23, 128.08, 127.49, 127.40, 126.07, 125.85 (C-H, aromatic), 101.02 (quaternary, oxazolidine), 79.00, 73.71 (CHO), 61.36, 55.00 (CH$_2$N); (Note Schiff base-oxazolidine tautomerism); IR (KBr): 3500 - 3100, 1617.9, 1490.2, 1444.5, 1316.7, 1093.8, 1060.4, 1026.6, 689.0, 542.3, 461.3 cm$^{-1}$, MS (EI): 301 (M$^+$), 283 (M-H$_2$O), 194 (M - BnOH), 91 (bp); m.p. = 148 - 151 °C.
5.4 Synthesis of Mosher Esters 6 and 6'

\((1R,2R)-2-[N-(Diphenylmethylene)amino]-1-O-benzoyl-1-phenylpropan-1-ol \ (4'):\)

To a stirred solution of \((1R,2R)-2-[N-(diphenylmethylene)amino]\)-1-phenylpropan-1-ol (710 mg, 2.25 mmol), in dry pyridine (5 mL) was added DMAP (cat) and benzoyl chloride (8.6 mmol, 3.8 eq). The reaction was stirred under argon overnight at RT. After pouring onto NaHCO\(_3\) (sat'd) and extracting with three volumes of CH\(_2\)Cl\(_2\), the combined organic layers were dried over K\(_2\)CO\(_3\), filtered, and removed under reduced pressure. Pure product was isolated via flash chromatography (756 mg, 1.8 mmol, 80%).

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.1 - 8.0 (m, 2 H), 7.6 - 7.2 (m, 16 H), 7.05 - 6.95 (m, 2 H), 6.12 (d, 1 H, \(J = 7.2\) Hz), 3.99 - 3.88 (m, 1 H), 1.11 (d, 3 H, \(J = 6.4\) Hz); \(^{13}\)C NMR APT (CDCl\(_3\)): \(\delta\) 165.51 (quaternary, ester), 139.84, 138.55, 136.79 (quaternary, aromatic), 132.74 (CH, aromatic), 130.52 (quaternary, aromatic), 129.84, 129.59, 128.47, 128.31, 128.20, 127.94, 127.64, 127.49 (CH, aromatic), 80.56 (CHO), 61.74 (CHN), 18.57 (CH\(_3\)); IR (Neat): 1721.7, 1626.2, 1449.5, 1271.5, 1111.9, 1069.8, 1026.3, 762.6, 699.7 cm\(^{-1}\); \([\alpha]_D\) = - 25.5 \(^{\circ}\) (c = 5.1, CHCl\(_3\)).

\((1S,2S)-2-[N(Diphenylmethylene)amino]-1-O-benzoyl-1-phenylpropan-1-ol \ (4):\)

Prepared similarly to 4' above. Obtained 217 mg isolated product (0.52 mmol, 75 % yield) after flash chromatography (20% EtOAc in hexane as eluant). \([\alpha]_D\) = + 25.2 \(^{\circ}\) (c = 5.1, CHCl\(_3\)).
(1R,2R)-2-[N-(Benzoyl)amino]-1-phenylpropan-1-ol (5'):

A solution of 4' (262 mg, 0.623 mmol), PPTS (313 mg, 1.2 mmol, 2 eq), in 2 mL of THF : H₂O (10:1) was stirred at RT for 5 h. After 5 h the reaction was quenched by pouring onto 5 mL NaHCO₃ (sat'd). The aqueous layer was extracted with CH₂Cl₂ (3 X 10 mL). The combined organic layers were dried (K₂CO₃) and evaporated under reduced pressure. Pure product was chromatographed using 17% acetone in CH₂Cl₂ to provide 80.5 mg (0.31 mmol, 50% yield).

¹H NMR (CDCl₃): δ 7.75 - 7.65 (m, 2 H), 7.5 - 7.2 (m, 8 H), 6.38 (d, 1 H, J = 7.6 Hz), 4.77 (d, 1 H, J = 5.4 Hz ), 4.46 - 4.33 (m, 1 H), 3.46 (s, 1 H), 1.24 (d, 3 H, J = 6.7 Hz); ¹³C NMR APT (CDCl₃): δ 168.07 (quaternary, amide), 141.61, 134.19 (quaternary, aromatic), 131.37, 128.37, 128.20, 127.58, 126.87, 126.26 (CH, aromatic), 76.82 (CHO), 51.69 (CHN), 17.43 (CH₃); [α]D = - 73.8 ° (c = 1.0, CHCl₃); m.p. = 128 - 130 °C.

(1S,2S)-2-[N-(Benzoyl)amino]-1-phenylpropan-1-ol (5):

Prepared similarly to 5' above. Obtained 70 mg isolated product (0.27 mmol, 67%) using flash chromatography (20% EtOAc/hexane as eluent). [α]D = + 74.3 ° (c = 1.0, CHCl₃).

(1R,2R)-2-[N-(Benzoyl)amino]-1-O-[(R)-(+-)-α-methoxy-α-(trifluoromethyl)phenylacetate]-1-phenylpropan-1-ol (6'):

A flame dried reaction vessel was charged with 29 mg of 5' (0.11 mmol), DCC (32 mg, 0.16 mmol, 1.4 eq), DMAP (cat) and 1 mL of CH₂Cl₂. A stock solution of (R)-(+-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid in CH₂Cl₂ (490 μL of 0.32 M, 0.16 mmol, 1.4 eq) was added dropwise. The reaction mixture was stirred at RT under Ar for 24 h. The dicyclohexylurea by-product was removed by filtering through Celite and the pure product obtained (32 mg, 0.066 mmol, 60%) via flash chromatography (30% EtOAc in hexane).
$^1$H NMR (CDCl$_3$): $\delta$ 7.75 - 7.65 (m, 2 H), 7.5 - 7.2 (m, 13 H), 6.12 (d, 1 H, 9.3 Hz), 6.03 (d, 1 H, J = 6.1 Hz), 4.77 - 4.68 (m, 1 H), 3.48 (d, 1 H, J = 1.1 Hz), 1.20 (d, 3 H, J = 6.8 Hz); $^{13}$C NMR (CDCl$_3$): $\delta$ 166.60, 165.81, 135.84, 133.99, 131.61, 129.58, 128.81, 128.80, 128.58, 128.52, 128.34, 127.29, 126.96, 126.76, 79.97, 55.44, 49.09, 17.60; IR (Neat): 1747.7, 1638.5, 1544.3, 1271.1, 1169.6, 1017.1, 690.4 cm$^{-1}$; $[\alpha]_D$ = - 25.8° (c = 1.6, CHCl$_3$).

$(1S,2S)$-2-[N-(Benzoyl)amino]–1-O–[(R)-(+)–$\alpha$-methoxy–$\alpha$-(trifluoromethyl)phenylacetate]–1-phenylpropan-1-ol (6):

Prepared similarly to 6'. Obtained 30 mg of isolated product (0.061 mmol, 63% yield) using flash chromatography for purification (30% EtOAc in hexanes as eluent).

$^1$H NMR (CDCl$_3$): $\delta$ 7.7 - 7.6 (m, 2 H), 7.45 - 7.20 (m, 13 H), 6.12 (d, 1 H, 5.6 Hz), 6.09 (d, 1 H, J = 6.3 Hz), 4.74 - 4.65 (m, 1 H), 3.44 (d, 1 H, J = 0.8 Hz), 1.19 (d, 3 H, J = 6.8 Hz).
5.5 Synthesis of 1-lodo-*trans*-alkenes (7a-e)

1-lodo-*trans*-hexene (7a):

A flame dried reaction vessel was charged with 7.18 g 1-hexyne (88 mmol) and 100 mL of dry hexanes. The solution was stirred vigorously at room temperature under argon while 40 mL of 2.2 M DIBAL in hexanes (88 mmol) was added over 2 h. The reaction mixture was then heated for 2 h at 60 °C. After cooling to RT the solvents were removed under reduced pressure. The resulting oil was taken up in approximately 100 mL THF. The solution was then chilled to -78 °C and 22.65 g I₂ in 60 mL THF was added dropwise via syringe. Upon completion of I₂ addition the reaction mixture was removed from the -78 °C bath and allowed to stand at RT for approximately 18 h. The THF was removed under reduced pressure. The residue was dissolved in 20 - 30 mL hexanes. The diisobutylalane was decomposed by cautious addition of 38% HCl. After the initial exothermic reaction had subsided, the mixture was poured onto 38% HCl and ice. The product was then extracted with three volumes of hexanes. The combined extracts were washed with Na₂S₂O₃, then saturated NaHCO₃. After drying over K₂CO₃, the solvent was removed by rotary evaporation and the crude product purified via flash chromatography (10.5 g, 50 mmol, 57%).

¹H NMR (CDCl₃): δ 6.5 (dt, 1 H, J = 7.2, 14.3 Hz), 6.0 (dt, 1 H, J = 1.4, 14.3 Hz), 2.1 - 2.0 (m, 2 H), 1.5 - 1.3 (m, 4 H), 0.9 (t, 3 H, 5.6 Hz); IR (Neat): 2956.5, 2926.3, 2857.5, 1605.3, 1464.2, 1378.8, 948.9, 920.9, 729.5, 658.6 cm⁻¹.

All other 1-lodo-*trans*-alkenes were synthesized following this procedure. Yields are given in parentheses.
1-iodo-trans-heptene (7b):

(5.9 g, 26 mmol, 73%)

$^1$H NMR (CDCl$_3$): $\delta$ 6.5 (dt, 1 H, $J = 7.3$, 14.3 Hz), 6.0 (dt, 1 H, $J = 1.4$, 14.3 Hz), 2.1 - 2.0 (m, 2 H), 1.5 - 1.2 (m, 6 H), 0.9 (t, 3 H, $J = 6.7$ Hz);

IR (Neat): 2926.1, 2855.7, 1605.2, 1465.3, 1377.5, 1208.5, 1173.6, 939.9, 725.4, 660.3 cm$^{-1}$.

1-iodo-trans-decene (7c):

(5.3 g, 16.5 mmol, 75%)

$^1$H NMR (CDCl$_3$): $\delta$ 6.5 (dt, 1 H, $J = 7.2$, 14.3 Hz), 6.0 (dt, 1 H, $J = 1.4$, 14.3 Hz), 2.1 - 2.0 (m, 2 H), 1.5 - 1.3 (m, 12 H), 0.9 (t, 3 H, $J = 7$ Hz);

IR (Neat): 2924.8, 2853.6, 1605.3, 1464.9, 1207.4, 945.7, 721.5, 660.0 cm$^{-1}$.

1-iodo-trans-pentadecene (7d):

(6.11 g, 18.2 mmol, 87%)

$^1$H NMR (CDCl$_3$): $\delta$ 6.51 (dt, 1 H, $J = 7.2$, 14.3 Hz), 5.96 (dt, 1 H, $J = 1.4$, 14.3 Hz), 2.1 - 2.0 (m, 2 H), 1.26 (bs, 22 H), 0.88 (t, 3 H, $J = 7$ Hz);

IR (Neat): 2922.5, 2852.8, 1457.0, 1375.8, 943.3, 720.8, 630.0 cm$^{-1}$.

1-iodo-trans-tetradecene (7e):

(4.5 g, 14.0 mmol, 80%)

$^1$H NMR (CDCl$_3$): $\delta$ 6.3 (dt, 1 H, $J = 7.1$, 14.3 Hz), 6.0 (dt, 1 H, $J = 1.4$, 14.3 Hz), 2.1 - 2.0 (m, 2 H), 1.5 - 1.2 (m, 20 H), 0.9 (t, 3 H, $J = 7$ Hz);

IR (Neat): 2923.5, 2852.9, 1605.8, 1465.4, 1377.1, 1191.7, 943.7, 720.3, 660.3 cm$^{-1}$.
5.6 Generation of 1-Lithio-trans-alkenes in Hydrocarbon Solvent (8a-d and 9)

**Preparation of 1-Lithio-trans-alkenes:**

To a flame dried reaction flask under argon were added 1.0 mmol of 1-iodo-trans-alkene and 2 mL freshly distilled hexanes. tBuLi was then added dropwise (2.2 mmol, 2.2 eq) with vigorous stirring. The mixture was stirred 30 min to 1 h at RT before use.

**Synthesis of 8a-d**

After stirring approximately 1 h at RT the 1-lithio-trans-alkenes were transferred to a chilled (0 °C) solution of benzaldehyde (212 mg, 2.0 mmol) in dry hexanes. Addition of alkenyllithium required approximately 30 min and was performed using a mechanical syringe pump.

After the combined reagents had stirred at RT for 1 h, the reaction mixture was quenched by pouring onto saturated NaHCO₃. The crude product was extracted into ether. The combined organic layers were dried (K₂CO₃) and removed under reduced pressure. Pure product was obtained after flash chromatography (134 mg, 0.71 mmol, 71%).

**1-Phenyl-2-hepten-1-ol (8a):**

(134 mg, 0.71 mmol, 71%)

$^1$H NMR (CDCl₃): δ 7.4 - 7.2 (m, 5 H), 5.83 - 5.64 (m, 2 H), 5.17 (d, 1 H, J = 6.2 Hz), 2.10 - 2.02 (m, 2 H), 1.84 - 1.78 (bs, 1 H), 1.44 - 1.20 (m, 4 H), 0.88 (t, 3 H, J = 7 Hz).
**1-Phenyl-2-undecen-1-ol (8c):**

(182 mg, 0.74 mmol, 74%)

$^1$H NMR (CDCl$_3$): $\delta$ 7.4 - 7.2 (m, 5 H), 5.82 - 5.61 (m, 2 H), 5.17 (d, 1 H, $J = 6.2$ Hz), 2.10 - 2.02 (m, 2 H), 1.9 (s, 1 H), 1.26 (bs, 12 H), 0.88 (t, 3 H, $J = 7$ Hz);

$^{13}$C NMR APT (CDCl$_3$): $\delta$ 143.40 (quaternary, aromatic), 132.70, 132.20 (CH, vinyl), 128.34, 127.34, 126.11 (CH, aromatic), 75.09 (CHO), 32.15, 31.83, 29.39, 29.21, 29.16, 29.04, 22.63 (CH$_2$), 14.07 (CH$_3$).

**1-Phenyl-2-hexadecen-1-ol (8d):**

(234 mg, 0.77 mmol, 77%)

$^1$H NMR (CDCl$_3$): $\delta$ 7.4 - 7.2 (m, 5 H), 5.8 - 5.6 (m, 2 H), 5.14 (d, 1 H, $J = 6.3$ Hz), 2.10 - 2.02 (m, 2 H), 1.38 (s, 1 H), 1.26 (bs, 22 H), 0.88 (t, 3 H, $J = 7$ Hz);

$^{13}$C NMR APT (CDCl$_3$): $\delta$ 143.37 (quaternary, aromatic), 132.67, 132.17 (CH, vinyl), 128.31, 127.32, 126.10 (CH, aromatic), 75.09 (CHO), 32.13, 31.86, 29.62, 29.48, 29.42, 29.30, 29.16, 29.01, 28.54, 22.63 (CH$_2$), 14.07 (CH$_3$).

**Synthesis of 9**

**E-1-Deuteropentadecene (9):**

E-1-Iodopentadecene (245 mg, 0.73 mmol) was passed through a short column of Al$_2$O$_3$ and dissolved in 2 mL dry hexanes. tBuLi (0.9 mL, 1.53 mmol, 2.1 eq) in pentane was then added dropwise. The reaction mixture was stirred 1 h at RT and was then quenched by dropwise addition of D$_2$O. Deuterated product was obtained in quantitative yield (153 mg, 0.73 mmol) by extracting the aqueous layer with Et$_2$O, drying (K$_2$CO$_3$), and solvent removal under reduced pressure.

$^1$H NMR (CDCl$_3$): $\delta$ 5.76 (dt, 1 H, $J = 6.2$, 17 Hz), 4.92 (d, 1 H, $J = 17$ Hz), 2.05 - 1.95 (m, 2 H), 1.25 (bs, 22 H), 0.88 (t, 3 H, $J = 6.5$ Hz).
5.7 Synthesis of N-Diphenylmethylene-Protected Threo-Sphingosines (10a-d and 11a-d)

**Method A (2 eq DIBAL):**

The Schiff base ester (1.0 mmol) was dissolved in 10 mL of dry CH₂Cl₂ and cooled to -78 °C under an argon atmosphere. Two equivalents of DIBAL were then added via gas-tight syringe (4.0 mL of 0.5 M DIBAL in hexanes) over 1.5 h. The reaction was stirred 15 min before three equivalents of alkenyllithium was added in one portion. The light yellow solution was stirred an additional 15 min at -78 °C, then warmed to room temperature. After stirring at room temperature for 3 h the reaction was quenched by pouring onto 15 mL of saturated NaHCO₃. An additional 20 mL of CH₂Cl₂ was used in several portions to ensure complete transfer. (Note: It is recommended that these solvent proportions be used in order to avoid the formation of an intractable emulsion). The aqueous layer was extracted with two additional 20 mL portions of CH₂Cl₂. The combined organic layers were dried over K₂CO₃, then filtered through Celite and evaporated under reduced pressure. Product was purified via flash chromatography. Solvent systems used for chromatography and yields for the two methods are listed in parentheses.

**Method B (DIBAL : TRIBAL):**

A flame dried reaction vessel was charged with 1.0 mmol of Schiff base ester and 10 mL of freshly distilled CH₂Cl₂. After chilling at -78 °C under argon for approximately 30 min, 1.1 equivalent of DIBAL : TRIBAL (1:1) was added (2.2 mL of 0.5 M solution in hexanes) via syringe pump. Addition required approximately 15 min. After addition was complete, 3 equivalents of alkenyllithium was added in one portion. The reaction was allowed to stir for 5 - 10 min at -78 °C, then warmed to RT. After stirring 1 h at room temperature, the reaction was quenched by pouring
onto 15 mL of saturated NaHCO₃. An additional 20 mL CH₂Cl₂ was used to ensure complete transfer (Note: It is recommended that these solvent proportions be used in order to avoid the formation of an intractable emulsion). The aqueous layer was then extracted with two additional 20 mL portions of CH₂Cl₂. The combined organic layers were dried over K₂CO₃, filtered through celite, then removed by rotary evaporation. Product was purified via flash chromatography. Solvent systems used for chromatography and yields for the two methods are listed in parentheses.

(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-4-octadecen-3-ol

(10a):

(Oil, 78% yield (method B); chromatography eluent: 10% EtOAc in petroleum ether).

¹H NMR (CDCl₃): δ 7.70 - 7.65 (m, 2 H), 7.60 - 7.50 (m, 2 H), 7.3 - 7.1 (m, 6 H), 5.71 (dt, 1 H, J = 6.9, 15.2 Hz), 5.28 (dd, 1 H, J = 8.2, 15.3 Hz), 3.83 (t, 1 H, J = 8.3 Hz), 2.94 (dq, 1 H, J = 6.4, 8.3 Hz), 2.4 - 2.2 (bs, 1 H), 2.03 - 1.96 (m, 2 H), 1.25 (bs, 22 H), 1.18 (d, 3 H, J = 6.4 Hz), 0.88 (t, 3 H, J = 6.6 Hz);

¹³C NMR APT (CDCl₃): δ 145.80, 145.31 (quaternary, aromatic), 134.91, 129.93 (CH, vinyl), 128.69, 128.30, 128.08, 127.83, 127.61, 127.27, 126.92, 126.21, 125.36 (CH, aromatic), 99.22 (quaternary, oxazolidine), 87.28 (CHO), 59.52 (CHN), 32.18, 31.85, 29.60, 29.40, 29.30 29.02, 22.61 (CH₂), 15.77, 14.06 (CH₃); IR (Neat): 2923.9, 2852.9, 1489.1, 1450.2, 1378.1, 1232.6, 1067.5, 1029.3, 966.8, 749.2, 702.0, cm⁻¹; [α]D = + 75.8 ° (c = 2.7, CHCl₃).
(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-4-tridecen-3-ol (10b):

(Oil, 71% yield (method B); chromatography eluent: 10% EtOAc in petroleum ether).

$^1$H NMR (CDCl$_3$): $\delta$ 7.75 - 7.65 (m, 2 H), 7.60 - 7.50 (m, 2 H), 7.4 - 7.2 (m, 6 H), 5.71 (dt, 1 H, $J$ = 6.9, 15.2 Hz), 5.31 (ddt, 1 H, $J$ = 1.3, 8.3, 15.2 Hz), 3.83 (t, 1 H, $J$ = 8.3 Hz), 3.0 - 2.9 (m, 1 H), 2.5 - 2.3 (bs, 1 H), 2.1 - 1.9 (m, 2 H), 1.4 - 1.2 (m, 12 H), 1.18 (d, 3 H, $J$ = 6.4 Hz), 0.88 (t, 3 H, $J$ = 7 Hz); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 145.78, 145.31 (quaternary, aromatic), 135.00 (CH, vinyl), 133.17 (CH, aromatic), 129.96 (CH, vinyl), 128.67, 128.34, 128.11, 127.97, 127.84, 127.70, 127.61, 127.29, 126.95, 126.23, 125.37 (CH, aromatic), 99.23 (quaternary, oxazolidine), 87.29 (CHO), 59.53 (CHN), 32.18, 31.80, 29.33, 29.19, 29.04, 28.98, 22.60 (CH$_2$), 15.78, 14.10 (CH$_3$); IR (Neat): 3297.9, 2926.2, 1489.6, 1450.6, 1378.3, 1232.6, 1067.5, 1029.7, 967.7, 750.2, 702.8, 630.4 cm$^{-1}$; $[\alpha]_D^0 = +79.5^\circ$ (c = 2.8, CHCl$_3$).

(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-4-decen-3-ol (10c):

(Oil, 45% yield (method A), 72% yield (method B); chromatography eluent: 10% EtOAc in hexanes ).

$^1$H NMR (CDCl$_3$): $\delta$ 7.8 - 7.75 (m, 2 H), 7.70 - 7.65 (m, 2 H), 7.6 - 7.1 (m, 6 H), 5.71 (dt, 1 H, $J$ = 6.8, 15.2 Hz), 5.30 (ddt, 1 H, $J$ = 1.3, 8.2, 15.2 Hz), 3.83 (t, 1 H, $J$ = 8.2 Hz), 3.0 - 2.9 (m, 1 H), 2.5 - 2.3 (bs, 1 H), 2.1 - 1.9 (m, 2 H), 1.5 - 1.2 (m, 6 H), 1.18 (d, 3 H, $J$ = 6.4 Hz), 0.87 (t, 3 H, $J$ = 7 Hz); $^{13}$C NMR (CDCl$_3$): $\delta$ 145.81, 135.22, 128.61, 128.20, 127.93, 127.37, 127.02, 126.29, 125.42, 99.29, 87.38, 59.59, 32.21, 31.33, 28.71, 22.45, 15.84, 14.01; IR (Neat): 3296.2, 1450.4, 1232.9, 957.3, 750.0, 702.8, 630.2 cm$^{-1}$; $[\alpha]_D^0 = +84.3^\circ$ (c = 3, CHCl$_3$).
(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-4-nonen-3-ol (10d):
(Oil, 73% yield (method B); chromatography eluent: 10% EtOAc in petroleum ether)

$^1$H NMR (CDCl$_3$): $\delta$ 7.9 - 7.8 (m, 2 H), 7.8 - 7.6 (m, 2H), 7.6 - 7.2 (m, 6H), 5.71 (dt, 1 H, J = 6.8, 15.3 Hz), 5.30 (dd, 1 H, J = 8.3, 15.3 Hz), 3.8 (t, 1 H, J = 8.3 Hz), 3.0 - 2.9 (m, 1 H), 2.5 - 2.2 (bs, 1 H), 2.1 - 1.9 (m, 2 H), 1.4 - 1.2 (m, 4 H), 1.18 (d, 3 H, J = 6.3 Hz), 0.87 (t, 3 H, J = 7 Hz); $^{13}$C NMR (CDCl$_3$): $\delta$ 135.19, 130.05, 128.64, 128.22, 127.93, 127.05, 126.31, 125.43, 99.25, 87.41, 59.59, 31.95, 31.21, 22.18, 15.86, 13.90; IR (Neat): 2957.8, 2926.2, 1726.8, 1662.3, 1450.0, 1276.5, 1067.7, 1029.1, 968.0, 749.0, 702.4, 630.0 cm$^{-1}$; $[\alpha]_D = +64.6^\circ$ (c = 1.2, CHCl$_3$)

(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-1-O-(tert-butyldimethylsilyl)-4-octadecen-1,3-diol (11a):
(Oil, 78% yield (method B); chromatography eluent: 5% EtOAc in petroleum ether).

$^1$H NMR (CDCl$_3$): $\delta$ 7.7 - 7.65 (m, 2 H), 7.5 - 7.4 (m, 2 H), 7.3 - 7.1 (m, 6H), 5.67 (dt, 1 H, J = 6.7, 15.2 Hz), 5.24 (dd, 1 H, J = 8.4, 15.2 Hz), 4.28 (t, 1 H, J = 8.4 Hz), 3.84 (dd, 1 H, J = 3.0, 10.6 Hz), 3.60 (dd, 1 H, J = 1.7, 10.6 Hz), 3.10 - 3.0 (bs, 1 H), 2.9 - 2.8 (m, 1 H), 2.10 - 1.9 (m, 2 H), 1.3 - 1.1 (bs, 22 H), 0.9 - 0.8 (m, 12 H), 0.02 (s, 3 H), 0.00 (s, 3 H); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 145.55, 145.17 (quaternary aromatic), 134.99, 129.31 (CH, vinyl), 128.05, 127.84, 127.37, 127.08, 126.67, 125.72 (CH, aromatic), 99.46 (quaternary, oxazolidine), 80.82 (CHO), 65.21 (CH$_2$O), 59.41 (CHN), 32.21, 31.90, 29.66, 29.60, 29.45, 29.34, 29.08 (CH$_2$), 25.77 (CH$_3$, tBu), 22.66 (CH$_2$), 14.10 (CH$_3$), -5.52, -5.57 (SiCH$_3$); IR (Neat): 2925.5, 1463.5, 1450.1, 1254.1, 1122.4, 968.4, 837.4, 770.0, 750.4, 701.7, 631.3, 532.2 cm$^{-1}$; $[\alpha]_D = +46.7^\circ$ (c = 0.9, CHCl$_3$).
(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-1-O-(tert-butyldimethylsilyl)-4-tridecen-1,3-diol (11b):

(Oil, 65% yield (method B); chromatography eluent: 10% EtOAc in petroleum ether).

\(^1\)H NMR (CDCl\(_3\)): \(\delta 7.75 - 7.7 (m, 2 H), 7.5 - 7.4 (m, 2 H), 7.3 - 7.15 (m, 6 H), 5.66 (dt, 1 H, \(J = 6.7, 15.2 \) Hz), 5.24 (dd, 1 H, \(J = 8.4, 15.2 \) Hz), 4.29 (t, 1 H, \(J = 8.3 \) Hz), 3.84 (dd, 1 H, \(J = 3.3, 10.6 \) Hz), 3.6 (dd, 1 H, \(J = 2.1, 10.6 \) Hz), 3.20 - 3.0 (bs, 1 H), 2.95 - 2.85 (m, 1 H), 2.10 - 1.9 (m, 2 H), 1.4 - 1.15 (bs, 12 H), 0.9 - 0.75 (m, 12 H), 0.02 (s, 3 H), 0.0 (s, 3 H); \(^{13}\)C NMR APT (CDCl\(_3\)): \(\delta 145.49, 145.13\) (quaternary, aromatic), 134.90, 129.31 (CH, vinyl), 127.99, 127.81, 127.34, 127.05, 126.64, 125.67 (CH, aromatic), 99.44 (quaternary, oxazolidine), 80.79 (CHO), 65.17 (CH\(_2\)O), 59.35 (CHN), 32.16, 31.81, 29.36, 29.21, 29.03 (CH\(_2\)), 25.74 (CH\(_3\), tBu), 22.62, 18.13 (CH\(_2\)), 14.07 (CH\(_3\)), -5.52, -5.57 (SiCH\(_3\)); IR (Neat): 2926.8, 1465.8, 1450.7, 1254.1, 1121.7, 1065.8, 1009.9, 968.2, 837.4, 778.0, 750.6, 701.1, 631.4 cm\(^{-1}\); [\(\alpha\)]\(_D\) = + 41.9 \(^o\) (c = 2.8, CHCl\(_3\)).

(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-1-O-(tert-butyldimethylsilyl)-4-decen-1,3-diol (11c):

(Oil, 40% yield (method A), 60% (method B); chromatography eluent: 10% EtOAc in petroleum ether).

\(^1\)H NMR (CDCl\(_3\)): \(\delta 7.8 - 7.75 (m, 2 H), 7.65 - 7.6 (m, 2 H), 7.60 - 7.15 (m, 6 H), 5.66 (dt, 1 H, \(J = 6.7, 15.2 \) Hz), 5.23 (ddt, 1 H, \(J = 1.3, 8.4, 15.2 \) Hz), 4.38 (t, 1 H, \(J = 8.2 \) Hz), 3.83 (dd, 1 H, \(J = 3.0, 10.7 \) Hz), 3.60 (dd, 1 H, \(J = 1.6, 10.7 \) Hz), 3.21 - 3.1 (bs, 1 H), 2.92 - 2.86 (m, 1 H), 2.05 - 1.9 (m, 2 H), 1.4 - 1.2 (m, 6 H), 0.9 - 0.8 (m, 12 H), 0.02 (s, 3 H), 0.00 (s, 3 H); \(^{13}\)C NMR (CDCl\(_3\)): \(\delta 145.52, 135.08, 130.02, 129.23, 128.05, 127.84, 127.41, 127.08, 126.67, 125.70, 99.41, 80.82, 65.16, 59.36, 32.16, 31.27, 28.72, 25.89, 25.75, 22.45,
14.01, -5.57; IR (Neat): 2928.9, 1448.5, 1251.7, 1089.1, 960.8, 832.4, 781.1, 695.5 cm\(^{-1}\); \([\alpha]\)\(_D\) = + 51.3 ° (c = 0.9, CHCl\(_3\)).

\((2S,3S,4E)-2-[N-(\text{Diphenylmethylene})\text{amino}]\text{-}1-O-(\text{tert-butyldimethylsilyl})\text{-}4\text{-nonen-1,3-diol} \ (11d)\): (Oil, 60% yield (method B); chromatography eluent: 5% EtOAc in petroleum ether).

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.75 - 7.65 (m, 2 H), 7.50 - 7.40 (m, 2 H), 7.3 - 7.15 (m, 6 H), 5.67 (dt, 1 H, J = 6.8, 15.3 Hz), 5.25 (ddt, 1 H, J = 1.3, 7.1, 15.3 Hz), 4.30 (t, 1 H, J = 8.3 Hz), 3.85 (dd, 1 H, J = 3.3, 10.6 Hz), 3.61 (dd, 1 H, J = 2.1, 10.6 Hz), 3.15 - 3.0 (bs, 1 H), 2.94 - 2.85 (m, 1 H), 2.03 - 1.95 (m, 2 H), 1.4 - 1.2 (m, 4 H), 0.95 - 0.75 (m, 12 H), 0.03 (s, 3 H), 0.02 (s, 3 H); \(^{13}\)C NMR APT (CDCl\(_3\)): \(\delta\) 145.55, 145.20 (quaternary, aromatic), 134.97, 129.28 (CH, vinyl), 128.23, 128.05, 128.00, 127.86, 127.41, 127.11, 126.69, 125.73 (CH, aromatic), 99.47 (quaternary, oxazolidine), 80.85 (CHO), 65.21 (CHN), 59.42 (CH\(_2\)O), 31.89, 31.22 (CH\(_2\)), 25.78 (CH\(_3\), tBu), 22.13 (CH\(_2\)), 18.59 (quaternary, tBu), 13.87 (CH\(_3\)), -5.48, -5.54 (SiCH\(_3\)). IR (Neat): 2928.4, 1449.9, 1254.1, 1121.1, 969.3, 837.2, 777.1, 750.2, 701.7, 631.1 cm\(^{-1}\); \([\alpha]\)\(_D\) = + 55.5 ° (c = 3.2, CHCl\(_3\)).
5.8 Cleavage of the N-Diphenylmethylene Protecting Group to Yield *Threo*-Sphingosines (10a'-d' and 11a'-d')

Cleavage of Schiff base protecting group:

The Schiff base protected amino alcohol was dissolved in 2 mL of THF : 3% HCl (1:1). The solution was stirred at RT until TLC indicated that hydrolysis of the Schiff base was complete (usually 1 h). The reaction mixture was transferred to a separatory funnel and the aqueous layer washed with several volumes of CH₂Cl₂. The aqueous layer was then made basic by addition of 2 N NaOH. Product was extracted with several volumes of CH₂Cl₂. The combined organic layers were dried over K₂CO₃ and removed under reduced pressure. Isolated amino alcohols were obtained in approximately quantitative yield.

*(2S,3S,4E)-2-Amino-4-octadecen-3-ol* (10a'):

Solid; ¹H NMR (CDCl₃): δ 5.72 (dd, 1 H, J = 6.7, 15.4 Hz), 5.40 (dd, 1 H, J = 7.3, 15.4 Hz), 3.67 (t, 1 H, J = 7.3 Hz), 2.81 - 2.7 (m, 1 H), 2.7 - 2.5 (bs, 3 H), 2.10 - 2.0 (m, 2 H), 1.26 (bs, 22 H), 1.06 (d, 3 H, J = 6.5 Hz), 0.88 (t, 3 H, J = 7 Hz);

¹³C NMR APT (CDCl₃): δ 133.69, 130.44 (CH, vinyl), 77.36 (CHO), 51.33 (CHN), 32.28, 31.84, 29.59, 29.42, 29.28, 29.13, 22.60 (CH₂), 20.18, 14.03 (CH₃);

IR (KBr): 3500 - 3300, 3344.4, 3277.8, 2922.2, 2855.6, 1466.7, 1450.0, 1372.2, 1094.4, 1038.9, 961.1 cm⁻¹; [α]D = + 9.7 ° (c = 1.1, CHCl₃);

Anal. Calcd for C, 76.32; H, 13.07; N, 4.95; Found: C, 74.83; H, 13.31; N, 5.26; m.p. = 67 - 70 °C (shrinking at 65 °C).
(2S,3S,4E)-2-Amino-4-tridecen-3-ol  (10b'):

Waxy solid; $^1$H NMR (CDCl$_3$): $\delta$ 5.72 (dt, 1 H, $J = 6.7$, 15.4 Hz), 5.41 (dt, 1 H, $J = 7.0$, 15.4 Hz), 3.65 (t, 1 H, $J = 7.0$ Hz), 2.9 - 2.7 (m, 1 H), 2.30 - 2.15 (bs, 3 H), 2.10 - 2.0 (m, 2 H), 1.4 - 1.2 (m, 12 H), 1.10 (d, 3 H, $J = 6.5$ Hz), 0.88 (t, 3 H, $J = 7$ Hz); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 133.81, 130.34 (CH, vinyl), 77.32 (CHO), 51.33 (CHN), 32.27, 31.80, 29.36, 29.18, 22.60 (CH$_2$), 20.20, 14.04 (CH$_3$); IR (Neat): 3500 - 3100, 2924.5, 1559.0, 1457.3, 1377.2, 968.8 cm$^{-1}$; [$\alpha$]$_D^0 = +7.36^\circ$ (c = 0.4, CHCl$_3$); MS (Cl - isobutane): 214 (M + 1), 196 (M + 1 - H$_2$O); HRMS (Cl - isobutane), M + 1 = 214.2166 (calcld for C$_{13}$H$_{28}$NO (M + 1), 214.2171).

(2S,3S,4E)-2-Amino-4-decen-3-ol  (10c'):

Waxy solid; $^1$H NMR (CDCl$_3$): $\delta$ 5.72 (dt, 1 H, $J = 6.7$, 15.4 Hz), 5.41 (ddt, 1 H, $J = 1.2$, 7.0, 15.4 Hz), 3.63 (t, 1 H, $J = 7.0$ Hz), 2.85 - 2.73 (m, 1 H), 2.10 - 2.00 (m, 2 H), 2.15 - 1.77 (bs, 3 H), 1.44 - 1.20 (m, 6 H), 1.08 (d, 3 H, $J = 6.3$ Hz), 0.88 (t, 3 H, $J = 6.8$ Hz); $^{13}$C NMR (CDCl$_3$): $\delta$ 133.93, 130.35, 77.42, 51.3, 32.27, 31.36, 28.80, 22.45, 20.53, 14.01; IR (Neat): 3600 - 3200, 2925.4, 1581.5, 1456.1, 1378.0, 1094.1, 1037.5, 971.5 cm$^{-1}$; [$\alpha$]$_D^0 = +4.6^\circ$ (c = 0.9, CHCl$_3$); MS (Cl - isobutane): 172 (M + 1), 154 (M + 1 - H$_2$O); HRMS (Cl - isobutane), M + 1 = 172.1680 (calcld for C$_{10}$H$_{22}$NO (M + 1), 172.1701).

(2S,3S,4E)-2-Amino-4-nonen-3-ol  (10d'):

Oil; $^1$H NMR (CDCl$_3$): $\delta$ 5.73 (ddt, 1 H, $J = 0.8$, 6.7, 15.3 Hz), 5.41 (ddt, 1 H, $J = 1.4$, 7.0, 15.3 Hz), 3.64 (t, 1 H, $J = 6.7$ Hz), 2.82 - 2.72 (m, 1 H), 2.15 - 1.95 (m, 5 H), 1.40 - 1.25 (m, 4 H), 1.10 (d, 3 H, $J = 6.5$ Hz), 0.9 (t, 3 H, $J = 7$ Hz); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 133.61, 130.46 (CH, vinyl), 77.33 (CHO), 51.30 (CHN), 31.92, 31.24, 22.10 (CH$_2$), 20.08, 13.81 (CH$_3$); IR (Neat): 3500 - 3000, 2926.4, 1582.7, 1453.8, 1378.3, 1141.1, 1093.4, 1037.5, 970.0, 865.8, 730.1
cm⁻¹; [α]D = + 10.9 ° (c = 3.4, CHCl₃); MS (Cl - isobutane): 158 (M + 1), 140 (M + 1 - H₂O); HRMS (Cl - isobutane), M + 1 = 158.1544 (calcd for C₉H₂₀NO (M + 1), 158.1545).

(2S,3S,4E)-2-Amino-4-octadecen-1,3-diol  (D-three-sphingosine)

(11a'):
Solid;¹H NMR (CDCl₃): δ 5.75 (dt, 1 H, J = 7, 15.1 Hz), 5.46 (dd, 1 H, J = 6.2, 15.1 Hz), 3.99 (t, 1 H, J = 5.6 Hz), 3.71 - 3.65 (m, 1 H), 3.57 - 3.50 (m, 1 H), 2.79 - 2.75 (m, 1 H), 2.10 - 2.0 (m, 2 H), 1.8 - 1.5 (bs, 4 H), 1.25 (bs, 22 H), 0.88 (t, 3 H, J = 6.4 Hz); m.p. = 87 - 89 °C (Lit. 86 - 87 °C¹²f and 88 - 88.5 °C⁷b).

(2S,3S,4E)-2-Amino-4-tridecen-1,3-diol   (11b'):
Waxy solid;¹H NMR (CDCl₃): δ 5.75 (dt, 1 H, J = 6.9, 15.4 Hz), 5.4 (dd, 1 H, J = 6.7, 15.4 Hz), 4.04 (t, 1 H, J = 6.1 Hz), 3.70 (dd, 1 H, J = 3.4, 11 Hz), 3.56 (dd, 1 H, J = 6.2, 11Hz), 3.15 - 2.90 (bs, 4 H), 2.90 - 2.80 (m, 1H), 2.15 - 2.0 (m, 2 H), 1.5 - 1.2 (m, 12 H), 0.9 (t, 3 H, J = 7 Hz); ¹³C NMR APT (CDCl₃): δ 134.05, 129.46 (CH, vinyl), 73.08 (CHO), 63.56 (CH₂O), 56.61 (CHN), 32.33, 31.83, 29.39, 29.24, 29.16, 22.60 (CH₂), 14.04 (CH₃); IR (Neat): 3600 - 3200, 2925.0, 1458.3, 1379.9, 1253.9, 1028.0, 968.7, 853.3 cm⁻¹; [α]D = - 4.0 ° (c = 0.63, CHCl₃); MS (Cl - isobutane): 230 (M + 1), 212 (M + 1 - H₂O), HRMS (Cl - isobutane), M + 1 = 230.2129 (calcd for C₁₃H₂₈NO₂ (M + 1), 230.2120).

(2S,3S,4E)-2-Amino-4-decen-1,3-diol  (11c'):
Waxy solid;¹H NMR (CDCl₃): δ 5.76 (dt, 1 H, J = 6.7, 15.4 Hz), 5.46 (dd, 1 H, J = 6.7, 15.4 Hz), 3.98 (t, 1 H, J = 6.0 Hz), 3.69 (dd, 1 H, J = 4.3, 10.7 Hz), 3.54 (dd, 1 H, J = 6.2, 10.7 Hz), 2.82 - 2.76 (m, 1 H), 2.15 - 2.0 (m, 2 H), 2.1 - 1.75 (bs, 4 H), 1.44 - 1.20 (m, 6 H), 0.88 (t, 3 H, J = 7 Hz); ¹³C NMR (CDCl₃): δ 133.99, 129.70, 73.60, 64.32, 56.45, 32.24, 31.36, 28.80, 22.45, 14.00; IR (Neat):
3500 - 3100, 2924.5, 1559.0, 1457.3, 1377.2, 968.8 cm\(^{-1}\); \([\alpha]_D = -2.10^\circ\) (c = 1.1, CHCl\(_3\)); MS (CI - isobutane): 188 (M + 1), 170 (M + 1 - H\(_2\)O) HRMS (CI - isobutane), M + 1 = 188.1672 (calcd for C\(_{10}\)H\(_{22}\)NO\(_2\) (M + 1), 188.1651).

**(2S,3S,4E)-2-Amino-4-nonen-1,3-diol (11d')**:  
Solid; \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 5.75 (ddt, 1 H, J = 1, 6.8, 15.4 Hz), 5.46 (ddt, 1 H, J = 1.3, 6.8, 15.4 Hz), 4.0 (t, 1 H, J = 6.0 Hz), 3.68 (dd, 1 H, J = 4.3, 10.8 Hz), 3.54 (dd, 1 H, J = 6.2, 10.8 Hz), 2.90 - 2.80 (m, 1 H), 2.34 - 2.15 (bs, 4 H), 2.15 - 2.0 (m, 2 H), 1.45 - 1.20 (m, 4 H), 0.9 (t, 3 H, J = 7 Hz); \(^{13}\)C NMR APT (CDCl\(_3\)): \(\delta\) 133.81, 129.79 (CH, vinyl), 73.62 (CHO), 64.33 (CH\(_2\)O), 56.41 (CHN), 31.95, 31.28, 22.19 (CH\(_2\)), 13.87 (CH\(_3\)); IR (KBr): 3600 - 3000, 2925.7, 1583.5, 1456.8, 1378.7, 1053.9, 1023.9, 969.5, 860.1, 583.1, 487.4 cm\(^{-1}\); \([\alpha]_D = -5.2^\circ\) (c = 0.9, CHCl\(_3\)); m.p. = 68 - 71 °C; MS (CI - isobutane): 174 (M + 1), 156 (M + 1 - H\(_2\)O); HRMS (CI - isobutane), M + 1 = 174.1492 (calcd for C\(_9\)H\(_{20}\)NO\(_2\) (M + 1), 174.1494); Anal. Calcd for C, 62.43; H, 10.98; N, 8.09; Found: C, 62.38; H, 11.17; N, 8.07.
5.9 Establishing Threo-Selectivity for the Sphingosine Synthesis (12a-c)

\((4S,5S)-5-((E)-Dec-1-en-1-yl)-4-methyl-2-oxazolidinone \) (12a):

To a flame dried reaction flask was added amino alcohol 10b' (119 mg, 0.56 mmol), carbonyldiimidazole (118 mg, 0.73 mmol), and 2 mL freshly distilled THF. The resulting solution was stirred for 2 hours at RT. The THF was evaporated, the resulting residue dissolved in Et\(_2\)O, washed (3 X 1N HCl, 1 X sat'd NaHC\(_2\)O\(_3\)), dried (K\(_2\)CO\(_3\)), and the solvent removed under reduced pressure to provide crude material. Chromatography (50% EtOAc/hexanes) provided 93 mg of purified product (70%, 0.39 mmol) as an oil.

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 5.85 (dd, 1 H, \(J = 6.8, 15.4\) Hz), 5.75 - 5.60 (bs, 1 H), 5.50 (ddt, 1 H, \(J = 7.9, 15.4, 1.4\) Hz), 4.43 (apparent t, 1 H, \(J = 7.6\) Hz), 3.70 - 3.50 (m, 1 H), 2.15 - 2.00 (m, 2 H), 1.25 (broad s, 12 H), 0.88 (t, 3 H, \(J = 6.6\) Hz);

\(^{13}\)C NMR APT (CDCl\(_3\)): \(\delta\) 159.31 (quaternary, carbonyl), 137.75, 125.31 (CH, vinyl), 85.21, 54.27 (CHX), 32.10, 31.80, 29.33, 29.17, 29.04, 28.63, 22.60 (CH\(_2\)), 19.22, 14.06 (CH\(_3\)); \([\alpha]\)\(_D\) = -29.9 \(^\circ\) (c = 1.6, CHCl\(_3\)).

\((4S,5S)-2,2\)-Diphenyl-5-((E)-dec-1-en-1-yl)-4-((tert-butyldimethylsiloxy)methyl)-N-(phenylcarbamoyl)oxazolidine (12b):

Compound 11b, (421 mg, 0.83 mmol) in dry pyridine (2 mL) was treated with phenyl isocyanate (1.8 mmol, 2.2 eq) and stirred at RT overnight. Pyridine and unreacted phenyl isocyanate were removed under reduced pressure. Chromatography (20% EtOAc/petroleum ether) provided 409 mg pure product (78% yield, 0.65 mmol) as an oil. \(^1\)H NMR (CDCl\(_3\)): \(\delta\) 7.70 - 7.60 (m, 2 H), 7.50 - 7.40 (m, 2 H), 7.4 - 7.20 (m, 7 H), 7.20 - 7.10 (m, 2 H), 6.90 - 6.80 (m, 2 H), 6.43 (broad s, 1 H), 5.83 (dt, 1 H, \(J = 6.4, 15.4\) Hz ), 5.66 (dd, 1 H, \(J = 7.1, 15.4\) Hz ), 4.25
(apparent t, 1 H, J = 7.7 Hz), 4.18 - 4.12 (m, 1 H), 3.92 (dd, 1 H, J = 3.9, 10.5 Hz), 3.84 (dd, 1 H, J = 4.7, 10.5 Hz), 2.10 - 2.0 (m, 2 H), 1.40 - 1.20 (broad s, 12 H), 0.90 - 0.80 (m, 12 H), 0.01 (s, 3 H), 0.00 (s, 3 H); $^{13}$C NMR APT (CDCl$_3$): δ 152.69 (quaternary, carbonyl), 141.70, 140.58, 138.37 (quaternary, aromatic), 136.63, 128.52 (CH, vinyl), 128.46, 128.37, 128.23, 128.12, 126.70, 122.76, 119.49 (CH, aromatic), 98.08 (quaternary, oxazolidine), 79.12 (CHO), 64.65 (CHN), 62.65 (CH$_2$O), 32.19, 31.74, 29.30, 29.08, 28.69 (CH$_2$), 25.80 (CH$_3$, tBu), 22.54 (quaternary, tBu), 14.01 (CH$_3$), -5.40 (SiCH$_3$); IR (Neat): 1673.6, 1596.9, 1528.7, 1441.9, 1332.1, 1249.5, 1102.7, 836.9, 751.6, 700.1 cm$^{-1}$; 

$\left[\alpha\right]_D = -14.1^\circ$ (c = 1.2, CHCl$_3$).

**D-threo-Sphingosine Triacetate (12c):**

Compound 12c was synthesized from 11a' following the published procedure of Garner et al.$^{12f}$

$^1$H NMR (CDCl$_3$): δ 5.77 (dt, 1 H, J = 6.6, 14.2 Hz), 5.64 (d, 1 H, J = 9.7 Hz), 5.40 (m, 2 H), 4.43 - 4.37 (m, 1 H), 4.08 (dd, 1 H, J = 2, 5.5 Hz), 2.08 - 1.98 (m, 11 H, contains three singlets at 2.08, 2.07, 2.00), 1.25 (bs, 22 H), 0.88 (t, 3 H, J = 6.6 Hz); $^{13}$C NMR APT (CDCl$_3$): δ 170.54, 169.96, 169.75 (quaternary, acetate), 137.17, 123.99 (CH, vinyl), 72.94 (CHO), 62.97 (CH$_2$O), 50.72 (CHN), 32.15, 31.79, 29.54, 29.45, 29.30, 29.21, 29.00, 28.68 (CH$_2$), 23.10 (CH$_3$, acetate), 22.57 (CH$_2$), 20.95, 20.63 (acetate CH$_3$), 13.98 (CH$_3$); IR (Neat): 1747.1, 1653.8, 1540.3, 1456.8, 1371.1, 1231.8, 1045.4, 968.5 cm$^{-1}$; $\left[\alpha\right]_D = +8.2^\circ$ (c = 2.2, CHCl$_3$); Lit. +8.43$^\circ$ $^{31}$ and +8.78$^\circ$ (c = 1.2, CHCl$_3$).$^{36b}$
5.10 Synthesis of Mosher Esters 15 and 15' 

\((2S,3S,4E)-2-[N-(\text{Diphenylmethylene})\text{amino}]\text{-3-O-benzoyl-4-tridecen-3-ol}\) (13):

To a stirred solution of 10b (150 mg, 0.40 mmol) and DMAP (cat) in 2 mL dry pyridine was added 400 \(\mu\)L of benzoyl chloride. The reaction was stirred at RT overnight before quenching with NaHCO\(_3\) (sat'd). The aqueous layer was extracted several times with CH\(_2\)Cl\(_2\). The combined organic layers were dried (K\(_2\)CO\(_3\)), filtered through Celite, and concentrated under reduced pressure. Crude product was purified via flash chromatography (15% EtOAc in hexane as eluent) to yield 161 mg pure product (0.33 mmol, 84%).

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 8.05 - 7.95 (m, 2 H), 7.6 - 7.1 (m, 13 H), 5.87 (dt, 1 H, \(J = 7, 15.4\) Hz), 5.63 (tt, 1 H, \(J = 7.5\) Hz), 5.44 (dd, 1 H, \(J = 7.8, 15.4\) Hz), 3.73 - 3.68 (m, 1 H), 2.10 - 1.98 (m, 2 H), 1.23 (bs, 15 H), 0.86 (t, 3 H, \(J = 7\) Hz);

\(^{13}\)C NMR APT (CDCl\(_3\)): \(\delta\) 167.69, 165.34 (quaternary, ester and imine), 139.90, 136.78 (quaternary aromatic), 136.41, 132.47 (CH, vinyl), 130.73, 129.69, 129.43, 128.40, 128.25, 128.11, 128.03, 127.81, 127.72, 125.52 (CH, aromatic), 79.24 (CHO), 60.36 (CHN), 32.26, 31.70, 29.24, 29.09, 28.98, 28.76, 22.51 (CH\(_2\)), 18.16, 13.98 (CH\(_3\)); IR (Neat): 1718.5, 1624.7, 1446.9, 1263.3, 1111.6, 964.7, 696.0 cm\(^{-1}\); \([\alpha]_D = -2.4^\circ\) (c = 1.1, CHCl\(_3\)).

\((2R,3R,4E)-2-[N-(\text{Diphenylmethylene})\text{amino}]\text{-3-O-benzoyl-4-tridecen-3-ol}\) (13'):

To a stirred solution of 10b' (243 mg, 0.645 mmol) and DMAP (cat) in 2 mL dry pyridine was added 650 \(\mu\)L of benzoyl chloride. The reaction was stirred at RT overnight before quenching with NaHCO\(_3\) (sat'd). The aqueous layer was extracted several times with CH\(_2\)Cl\(_2\). The combined organic layers were dried (K\(_2\)CO\(_3\)), filtered
through Celite, and concentrated under reduced pressure. Crude product was purified via flash chromatography (15% EtOAc in hexane as eluent) to yield 204 mg pure product (0.423 mmol, 66%).

\[ \alpha \] = + 2.3 ° (c = 1.1, CHCl_3).

**\( 2S,3S,4E \)-2-[N-(Benzoyl)amino]-4-tridecen-3-ol (14):**

A solution of 13 (154 mg, 0.320 mmol), PPTS (161 mg, 0.620 mmol, 2 eq), in 2 mL of THF : H_2O (10:1) was stirred at RT. After 8 h the reaction was quenched by pouring onto 5 mL NaHCO_3 (sat'd). The aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure. Crude product was chromatographed using 20% acetone in CH_2Cl_2 to provide 42 mg of pure 14 (0.14 mmol, 44%).

\[ \alpha \] = + 3.9 ° (c = 2.3, CHCl_3).

\[ \text{H NMR (CDCl}_3\text{): } \delta \text{ 7.85 - 7.75 (m, 2 H), 7.6 - 7.3 (m, 3 H), 6.38 (d, 1 H, J = 8.2 Hz), 5.75 (dt, 1 H, J = 7, 15.4 Hz), 5.52 (dd, 1 H, J = 6.8, 15.4 Hz), 4.25 - 4.12 (m, 2 H), 2.45 (s, 1 H), 2.06 - 1.98 (m, 2 H), 1.30 (d, 3 H, J = 6.7 Hz), 1.23 (bs, 12 H), 0.87 (t, 3 H, J = 7 Hz); } \text{C NMR (CDCl}_3\text{): } \delta \text{ 167.69, 134.52, 133.93, 131.36, 129.52, 128.40, 126.91, 75.53, 50.06, 32.24, 31.81, 29.36, 29.13, 22.60, 17.52, 14.04; } \text{IR (Neat): 3573.7 - 3117.5, 1636.4, 1578.5, 1538.5, 1489.0, 1455.6, 968.5, 891.7, 710.6 cm}^{-1}; [\alpha] = + 3.9 ° (c = 2.3, CHCl_3).}

**\( 2R,3R,4E \)-2-[N-(Benzoyl)amino]-4-tridecen-3-ol (14'):**

A solution of 13' (118 mg, 0.245 mmol) and PPTS (124 mg, 2 eq) in 2 mL of THF : H_2O (10:1) was stirred at RT for 15 h. After 15 h the reaction was quenched by pouring onto 5 mL NaHCO_3 (sat'd). The aqueous layer was extracted with CH_2Cl_2 (3 X 10 mL). The combined organic layers were dried (K_2CO_3) and concentrated under reduced pressure. Crude product was chromatographed using 15% acetone in CH_2Cl_2 to provide 44 mg of pure 14' (0.14 mmol, 44%).

[\alpha] = - 3.8 ° (c = 2.3, CHCl_3).
(2S,3S,4E)-2-[N-(Benzoyl)amino]-1-O-[(R)-(+)−α-methoxy−α-(trifluoromethyl)phenylacetate]-tridecen-3-ol (15):

A flame dried reaction vessel was charged with 42 mg of 14 (0.14 mmol), DCC (40 mg, 0.19 mmol, 1.4 eq), DMAP (cat) and 1 mL of CH₂Cl₂. A stock solution of (R)-(+)−α-methoxy−α-(trifluoromethyl)phenylacetic acid in CH₂Cl₂ (600 µL of 0.32 M, 0.19 mmol, 1.4 eq) was added dropwise. The reaction mixture was stirred at RT under Ar for 84 h. After evaporating solvents, the crude reaction product was applied directly to a silica gel column and chromatographed using 30% EtOAc in hexane as eluent. Pure product was obtained in 62% yield (46 mg, 0.086 mmol, 62%).

1H NMR (CDCl₃): δ 7.7 - 7.6 (m, 2 H), 7.55 - 7.3 (m, 8 H), 6.11 (d, 1 H, J = 8.9 Hz), 5.92 (dt, 1 H, J = 7, 14 Hz), 5.60 - 5.50 (m, 2 H), 4.52 - 4.47 (m, 1 H), 3.53 (d, 3 H, J = 9 Hz), 2.08 - 2.00 (m, 2 H), 1.22 (m, 15 H), 0.87 (t, 3 H, J = 7 Hz); 13C NMR APT (CDCl₃): δ 166.25, 165.72 (quaternary, imine and ester), 139.20 (CH, vinyl), 134.11, 132.14 (quaternary aromatics), 131.58, 129.70, 128.58, 128.42, 127.36, 126.74, 123.78 (CH, aromatic), 79.63, 55.33, 47.92 (CHX), 32.30, 31.83, 29.36, 29.16, 29.06, 28.80, 22.63, (CH₂), 17.99, 14.07 (CH₃); IR (Neat): 1739.0, 1631.0, 1548.1, 1490.3, 1450.1, 1263.9, 1184.3, 1127.6, 1079.8, 1015.9, 993.3, 717.4, 695.4 cm⁻¹; [α]D = + 14.1 ° (c = 2.5, CHCl₃).

(2R,3R,4E)-2-[N-(Benzoyl)amino]-1-O-[(R)-(+)−α-methoxy−α-(trifluoromethyl)phenylacetate]-tridecen-3-ol (15): A flame dried reaction vessel was charged with 59 mg of 14' (0.195 mmol), DCC (56 mg, 0.272 mmol, 1.4 eq), DMAP (cat) and 1 mL of CH₂Cl₂. A stock solution of (R)-(+)−α-methoxy−α-(trifluoromethyl)phenylacetic acid in CH₂Cl₂ (900 µL of 0.32 M, 0.272 mmol, 1.4 eq) was added dropwise. The reaction mixture was stirred at RT under Ar for 80 h. After evaporating solvents, the crude reaction product was
applied directly to a silica gel column and chromatographed using 25% EtOAc in hexane as eluant. Pure product was obtained in 60% yield (63 mg, 0.118 mmol).

$^1$H NMR (CDCl$_3$): $\delta$ 7.7 - 7.6 (m, 2 H), 7.5 - 7.3 (m, 8 H), 6.16 (d, 1 H, $J = 9.03$ Hz), 5.88 (dt, 1 H, $J = 7, 14$ Hz), 5.50 - 5.36 (m, 2 H), 4.53 - 4.48 (m, 1 H), 3.51 (d, 3 H, $J = 1$ Hz), 2.05 - 1.97 (m, 2 H), 1.31 (d, 3 H, $J = 8$ Hz), 1.22 (bs, 12 H), 0.87 (t, 3 H, $J = 7$ Hz); $^{13}$C NMR (CDCl$_3$): $\delta$ 166.60, 165.81, 138.90, 134.08, 131.96, 131.58, 129.61, 128.58, 128.37, 127.37, 126.75, 123.49, 79.79, 55.36, 47.97, 32.24, 31.80, 29.34, 29.15, 29.01, 28.71, 22.61, 17.98, 14.05.
5.11 Comparison of Boc Protection With O'Donnell's Benzopenone Schiff Base (17)

\((2S,3S,4E)-2-[N-(\text{tert-Butyloxy})\text{carbonyl})\text{amino}]\) -1-O-(\text{tert-butyldimethylsilyl})-4-octadecen-1,3-diol \((17):\)

To a stirred solution of compound \(16^{34}\) (352 mg, 1.1 mmol) in \(\text{CH}_2\text{Cl}_2\) (10 mL) at -78 °C was added 2.6 mL of 0.45 M (1:1) DIBAL : TRIBAL (1.2 mmol, 1.1 eq.). \(\text{trans}-1\)-Pentadecenyllithium was then added (3.3 mmol) in one portion. The resulting solution was stirred for two hours at -26 °C. After warming to RT the reaction was quenched by pouring onto 15 mL NaHCO\(_3\) (sat'd). Crude product was extracted with \(\text{CH}_2\text{Cl}_2\) (3 X 20 mL). After drying (\(\text{K}_2\text{CO}_3\)), the organic solvents were removed under reduced pressure. Reaction products were isolated (284 mg, 0.55 mmol, 52%) via flash chromatography (15% EtOAc in petroleum ether).

\(^1\text{H} \text{NMR (CDCl}_3\): \(\delta 5.74 \text{ (dt, 1 H, } J = 7, 15.4 \text{ Hz}), 5.46 \text{ (dd, 1 H, } J = 6.6, 15.4 \text{ Hz)}, 5.12 \text{ (d, 1 H, } J = 8.4 \text{ Hz)}, 4.42 - 4.36 \text{ (m, 1 H)}, 3.93 - 3.74 \text{ (m, 2 H)}, 3.61 - 3.53 \text{ (m, 1 H)}, 3.4 - 3.2 \text{ (bs, 1 H)}, 2.15 - 2.0 \text{ (m, 2 H)}, 1.45 \text{ (s, 9 H)}, 1.25 \text{ (bs, 22 H)}, 0.90 \text{ (m, 12 H)}, 0.07 \text{ (s, 6 H)}; \(^{13}\text{C} \text{NMR APT: } \delta 155.92 \text{ (quaternary, BOC carbonyl)}, 132.76, 129.13 \text{ (CH, vinyl)}, 78.91 \text{ (quaternary, BOC tBu)}, 72.50 \text{ (CHO)}, 64.14 \text{ (CH}_2\text{O)}, 54.89 \text{ (CHN)}, 32.13, 31.74, 29.50, 29.43, 29.33, 29.18, 29.01 \text{ (CH}_2\text{)}, 28.16 \text{ (CH}_3\text{, tBu)}, 25.61 \text{ (CH}_3\text{, tBu)}, 22.48 \text{ (CH}_2\text{)}, 17.92 \text{ (quaternary, Si-tBu)}, 13.91 \text{ (CH}_3\text{)}, -5.78 \text{ (SiCH}_3\text{)}; \text{IR (Neat): } 1720.3, 1698.8, 1504.4, 1470.9, 1390.9, 1366.3, 1253.7, 1172.5, 1107.8, 967.5, 837.1, 777.4 \text{ cm}^{-1}.

Diastereoselectivity (6.4 : 1) was determined by integrating vinyl peaks in the \(^{13}\text{C} \text{NMR}: \text{major (}\delta 132.75, 129.14\text{), minor (}\delta 132.64, 129.37\text{).}
5.12 Mechanistic Studies—Stereochemical Influence of the Ester Moiety

The N-(diphenylmethylene)amino-alanine esters were taken up in enough freshly distilled CH$_2$Cl$_2$ to make a 0.1 M reaction mixture. The solution was chilled to -78 °C for approximately 15 min then treated with 1.1 equivalents of DIBAL:TRIBAL (0.5 M in hexanes added at rates of approximately 8 mL h$^{-1}$). PhMgBr in either Et$_2$O or Et$_2$O : THF (1:1) was then added dropwise. The reaction mixture was allowed to stir 1 h at -78 °C followed by an additional hour at RT. The reaction was quenched by pouring onto NaHCO$_3$ (sat'd). The aqueous layer was washed with two equal volumes of CH$_2$Cl$_2$. The combined organic layers were removed under reduced pressure. The resulting crude oil was taken up in THF: 3% HCL (1:1, to make an approximately 1 M reaction mixture) and stirred at RT until TLC indicated complete consumption of the starting material. The THF was then removed under reduced pressure. The aqueous layer was made alkaline with addition of 2 N NaOH. The product was extracted with several volumes of CH$_2$Cl$_2$. The combined organic layers were dried over K$_2$CO$_3$ and the solvent removed under reduced pressure. Stereoselectivities were determined by integrating the diastereomeric C-1 methinyl protons (erythro: $\delta$ 4.53; threo: $\delta$ 4.24 ).
5.13 Mechanistic Studies—Synthesis of 18a and 18b

\((1S,2S)-2-[N-(\text{Diphenylmethylene})\text{amino}]-1\text{-ethoxy-1-siloxy-propane (18a) and (1R,2S)-2-[N-(\text{Diphenylmethylene})\text{amino}]-1\text{-ethoxy-1-siloxy-propane (6.5:1 18a and 18b mixture):}\)

To a stirred solution of 1a (283 mg, 1.0 mmol) in dry CH\(_2\text{Cl}_2\) (4 mL) at -78 °C was added 2.4 mL of 0.5 M DIBAL:TRIBAL (1:1) in hexanes (1.2 mmol, 1.2 eq) over 15 min. The resulting yellow solution was allowed to stir 72 h at -78 °C. TMS-imidazole (426 mg, 3 mmol) in CH\(_2\text{Cl}_2\) (2 mL) was then added. The reaction was stirred for 2 h at -78 °C followed by an additional h at RT. The yellow color persisted during the entire period at -78 °C, but was discharged as the reaction mixture came to RT. The clear solution was quenched by pouring onto 15 mL of saturated NaHCO\(_3\). The aqueous layer was washed with three 20 mL portions of CH\(_2\text{Cl}_2\) and the combined organic layers were then dried (K\(_2\text{CO}_3\)) and evaporated under reduced pressure. The product was purified via flash chromatography to yield 252 mg of an inseparable (6.5:1) mixture of 18a and 18b (0.71 mmol, 71%). \(^1\text{H} \text{NMR (CDCl}_3\):} \delta 7.65 - 7.55 (m, 2 H), 7.45 - 7.25 (m, 6 H), 7.2 - 7.1 (m, 2 H), 4.82 (d, 1 H, \(J = 6.4 \text{ Hz}\)), 3.8 - 3.55 (m, 1 H), 3.5 - 3.3 (m, 2 H), 1.14 (t, 3 H, \(J = 7 \text{ Hz}\)), 1.12 (d, 3 H, \(J = 6.4 \text{ Hz}\)), 0.15 (s, 6 H), 0.09 (s, 3 H); \(^{13}\text{C} \text{NMR APT (CDCl}_3\) 18a :} \delta 167.22 (quaternary, imine), 140.19, 137.02 (quaternary, aromatic), 129.61, 129.55, 128.31, 128.23, 128.15, 128.04, 127.96, 127.84, 127.76, 127.34 (CH, aromatic), 101.41 (quaternary, SiO-CH-O), 62.92 (CH\(_2\text{O}\), 62.56 (CHN), 17.59, 15.28 (CH\(_3\)), 0.59 (SiCH\(_3\)); IR (Neat): 1627.1, 1599.1, 1578.9, 1490.1, 1446.0, 1372.7, 1313.9, 1287.6, 1250.4, 1152.9, 1119.1, 1058.9, 1029.0, 952.9, 883.9, 840.3, 695.5, 647.9 cm\(^{-1}\); \([\alpha]D = +31.43^\circ (c = 4.4, \text{CHCl}_3)\); HRMS (Cl-isobutane): M + 1 = 356.2035 (C\(_{21}\text{H}_{30}\text{NSiO}_2\) = 356.2046).
(1S,2S)-2-[N-(Diphenylmethylene)amino]-1-ethoxy-1-siloxypropane and (1R,2S)-2-[N-(Diphenylmethylene)amino]-1-ethoxy-1-siloxypropane (2:1 18a and 18b mixture):

To a stirred solution of 1a (140 mg, 0.5 mmol) in dry CH₂Cl₂ (2 mL) at -78 °C was added 1.4 mL of 0.4 M DIBAL:TRIBAL:PhLi (1:1:1) in hexanes (0.56 mmol, 1.1 eq) over 15 min. The resulting solution was allowed to stir 1 h at -78 °C. TMS-imidazole (213 mg, 1.5 mmol) in CH₂Cl₂ (2 mL) was then added. The reaction was stirred an additional h at -78 °C followed by 1 h at RT. The reaction was quenched by pouring into 15 mL saturated NaHCO₃. The aqueous layer was washed with three 20 mL portions of CH₂Cl₂ and the combined organic layers were then dried (K₂CO₃) and evaporated under reduced pressure. Analysis of the crude ¹³C NMR revealed the two possible diastereomeric products were formed in a 2:1 ratio. 18b ¹³C NMR APT (CDCl₃): δ 166.95 (quaternary, imine), 139.81, 136.69 (quaternary, aromatic), 129.61, 129.55, 128.31, 128.23, 128.15, 128.04, 127.96, 127.84, 127.76, 127.34 (CH, aromatic), 101.32 (quaternary, SiO-CH-O), 67.68 (CH₂O), 62.85 (CHN), 17.45, 15.01 (CH₃), -0.52 (SiCH₃).

Preparation of DIBAL:TRIBAL:PhLi (1:1:1):

DIBAL : TRIBAL (5 mL of 0.5 M (1:1) in hexanes) was added to a flame dried reaction vessel and chilled to -78 °C. PhLi [1.4 mL of 1.8 M in cyclohexane : Et₂O (7:3)] was added while stirring at -78 °C. The mixture stirred 1 h at -78 °C, then was allowed to warm 1 h prior to adding to a solution of the Schiff base in CH₂Cl₂.
5.14 Mechanistic Studies—Kinetics of D:T Reduction

To a stirred solution of 1a (283 mg, 1.0 mmol) in dry CH₂Cl₂ (4 mL) at -78 °C was added 2.4 mL of 0.5 M DIBAL:TRIBAL (1:1) in hexanes (1.2 mmol, 1.2 eq) over 15 min. The resulting yellow solution was allowed to stir for varying amounts of time at -78 °C (12, 30 and 72 h). TMS-imidazole (426 mg, 3 mmol) in CH₂Cl₂ (2 mL) was then added. The reaction was stirred for 2 h at -78 °C followed by an additional h at RT. The yellow color persisted during the entire period at -78 °C, but was discharged as the reaction mixture came to RT. The clear solution was quenched by pouring onto 15 mL saturated NaHCO₃. The aqueous layer was washed with three 20 mL portions of CH₂Cl₂ and the combined organic layers were then dried (K₂CO₃), and evaporated under reduced pressure. A crude ¹H NMR was taken of this material without further purification. Integration of the methinyl resonance of 18a and b (δ 4.82) vs the CH₂ and CH-N resonances of the starting material (δ 4.16) was used to determine the extent of reaction:

Results of Reductions at Various Times

<table>
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<tr>
<th>Time</th>
<th>δ 4.16 : 4.82</th>
</tr>
</thead>
<tbody>
<tr>
<td>12h</td>
<td>1:1</td>
</tr>
<tr>
<td>30h</td>
<td>1:2</td>
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<tr>
<td>72 h</td>
<td>0:1</td>
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Mitsunobu Inversion of N-Diphenylmethylene-Protected Erythro β-Amino Alcohol 3a" to Provide Threo 19

A small quantity of compound 3a" (88 mg, 0.28 mmol) was azeotropically dried with benzene. Ph₃P (147 mg, 0.56 mmol, 2 eq) and cesium pivalate (110 mg, 0.47 mmol, 1.7 eq) were then added. The reagents were taken up in 1 mL of Et₂O (anhydrous) and stirred at RT under argon. DEAD (98 mg, 0.56 mmol, 2 eq) was then added dropwise while stirring. The reaction was allowed to stir overnight before filtering through Celite. Solvents were then evaporated and the crude product chromatographed (10% EtOAc in petroleum ether) via flash chromatography to yield 42 mg of pure product (0.10 mmol, 37%). When the reaction was conducted using THF as solvent, product was obtained in 23% yield (39 mg, 0.098 mmol).

¹H NMR (CDCl₃): δ 7.65 - 7.55 (m, 2 H), 7.45 - 7.40 (m, 2 H), 7.40 - 7.2 (m, 9 H), 7.1 - 7.0 (m, 2 H), 5.85 (d, 1 H, J = 7.7 Hz), 3.82 - 3.72 (m, 1 H), 1.15 (s, 9 H), 1.02 (d, 3 H, J = 6.5 Hz); ¹³C NMR APT (CDCl₃): δ 177.22, 167.60 (quaternary, imine and ester), 139.78, 138.93, 136.73 (quaternary, aromatic), 130.02, 129.88, 128.46, 128.37, 128.29, 128.14, 127.96, 127.80, 127.58, 127.40 (CH, aromatic), 80.03 (CHO), 61.62 (CHN), 38.68 (quaternary, tBu), 27.16 (CH₃, tBu), 18.46 (CH₃); IR (Neat): 2359.8, 1729.5, 1625.0, 1478.3, 1446.0, 1282.0, 1152.6, 762.0, 697.2, 668.0, 647.2, 366.7 cm⁻¹; [α]D = - 110° (c = 1.4, CH₂Cl₂).
5.16 Synthesis of p-Nitrophenyl Esters (20 and 26)

**p-Nitrophenyl Acetate (20):**

A flame dried reaction flask was charged with p-nitrophenol (1.4 g, 10 mmol) and 55 mL of Et₂O : Et₃N (10:1) and stirred at 0 °C under argon. Acetyl chloride (1.7 mL, 24 mmol) was then added dropwise via syringe while vigorously stirring. The resulting yellow slurry was allowed to react 1 h at RT at which time it was transferred to a separatory funnel containing saturated NaHCO₃. The organic layer was extracted two more times with NaHCO₃ (sat'd), dried over K₂CO₃, and filtered through celite. Solvents were removed via rotary evaporation. Crude material was recrystallized from 25% EtOAc in petroleum ether to afford 1.5 g (8.3 mmol, 83%) of pure product. ¹H NMR (CDCl₃): δ 8.28 (apparent d, 2 H, J = 9.1 Hz), 7.29 (apparent d, 2 H, J = 9.1 Hz), 2.36 (s, 3 H); ¹³C NMR APT (CDCl₃): δ 168.28 (quaternary, acetate), 155.19, 144.99 (quaternary, aromatic), 124.90, 122.29 (CH, aromatic), 20.80 (CH₃, acetate); m.p. = 75 - 78 °C.

**p-Nitrophenyl Stearate (26):**

A flame dried reaction vessel was charged with p-nitrophenol (384 mg, 2.76 mmol, 1.2 eq) and stearic acid (776 mg, 2.73 mmol, 1.2 eq). The reagents were taken up in 10 mL dry CH₂Cl₂ : THF (1:1) and stirred under argon at 0 °C. DCC was added (2.3 mL of 1.0 M DCC in CH₂Cl₂). The resulting solution was allowed to stir overnight at RT. The solvents were removed under reduced pressure. The resulting slurry was taken up in hexanes and passed through a plug of Celite to remove solid cyclohexylurea. After evaporating the filtrate, pure product was obtained via flash chromatography (20% EtOAc in petroleum ether) in 91% yield (840 mg, 2.1 mmol). ¹H NMR (CDCl₃): δ 8.27 (apparent d, 2 H, J = 9.2 Hz), 7.28 (apparent d, 2 H, J =
9.2 Hz), 2.60 (t, 2 H, J = 7.5 Hz), 1.80 - 1.70 (m, 2 H), 1.26 (bs, 28 H), 0.88 (t, 3 H, J = 7 Hz); $^1$H NMR APT (CDCl$_3$): δ 71.25 (quaternary, ester), 155.45, 145.14 (quaternary, aromatic), 125.10, 122.38 (CH, aromatic), 34.24, 31.86, 29.65, 29.54, 29.39, 29.30, 29.16, 28.98, 24.68, 22.63 (CH$_2$), 14.07 (CH$_3$).
Selective PPTS-catalyzed Cleavage of the Benzophenone Schiff Base (24 and 25)

(2S,3S,4E)-2-Amino-1-O-(tert-butyldimethylsilyl)-4-tridecen-1,3-diol (24):

To a stirred solution of 11b (837 mg, 1.65 mmol) in THF : H₂O (10:1) was added PPTS (828 mg, 3.30 mmol, 2 eq). The reaction was stirred for 4 h at RT, then quenched by pouring onto NaHCO₃ (sat’d). The product was extracted with several volumes of CH₂Cl₂. The combined organic layers were dried over K₂CO₃, then removed under reduced pressure. Pure product (313 mg, 0.912 mmol, 55%) was obtained after flash chromatography (10% MeOH in CH₂Cl₂).

¹H NMR (CDCl₃): δ 5.67 (dt, 1 H, J = 7, 15.2 Hz), 5.36 (dd, 1 H, J = 8.2, 15.2 Hz), 4.05 (t, 1 H, J = 8.2 Hz), 3.84 (dd, 1 H, J = 3, 10.6 Hz), 3.61 (dd, 1 H, J = 1.6, 10.6 Hz), 3.0 - 2.95 (m, 1 H), 2.5 - 2.2 (bs, 2 H), 2.06 - 1.97 (m, 2 H), 1.34 (s, 1 H), 1.24 (bs, 12 H), 0.95 - 0.86 (m, 12 H), 0.04 (s, 6 H); IR (Neat): 1462.2, 1255.7, 967.9, 836.4, 776.8 cm⁻¹.

(2S,3S,4E)-2-Amino-1-O-(tert-butyldimethylsilyl)-4-octadecen-1,3-diol (25):

Compound 11a (54 mg, 0.094 mmol) was subjected to the same procedure. Pure product (20 mg, 0.048 mmol, 52%) was obtained after flash chromatography (10% MeOH in CH₂Cl₂).

¹H NMR (CDCl₃): δ 5.67 (dt, 1 H, J = 6.8, 15.4 Hz), 5.35 (dd, 1 H, J = 6.7, 15.4 Hz), 3.91 (t, 1 H, J = 6.2 Hz), 3.62 (dd, 1 H, J = 4.1, 10 Hz), 3.54 (dd, 1 H, J = 5.3, 10 Hz), 2.70 - 2.64 (m, 1 H), 2.3 - 2.1 (bs, 3 H), 2.05 - 1.95 (m, 2 H), 1.19 (bs, 22 H), 0.86 - 0.69 (m, 12 H), 0.00 (s, 6 H); IR (Neat): 1731.8, 1464.1, 1361.1, 1255.4, 1103.7, 969.9, 836.6, 777.1, 668.2 cm⁻¹; [α]D = -4.0 ° (c = 1, CHCl₃).
Selective N-Acylation of Amino Alcohols (21 and 27)

(1\textsuperscript{R},2\textsuperscript{R})-2-[N-(Acetyl)amino]-1-phenylpropan-1-ol (21):

Method A:

A reaction vessel was charged with (1\textsuperscript{R},2\textsuperscript{R})-2-amino-1-phenylpropan-1-ol (27 mg, 0.18 mmol), p-nitrophenyl acetate (64 mg, 0.35 mmol) and HOBT (cat). Tetrahydrofuran (0.3 mL) was then added. The reaction was stirred for 15 h at RT at which time the solvents were removed under reduced pressure. The crude syrup thus obtained was applied directly to a flash silica gel column and chromatographed using 10% MeOH in CH\textsubscript{2}Cl\textsubscript{2} as eluent. Pure product was obtained in 96% yield (33 mg, 0.17 mmol). Note: Experiments indicate that DMF, DMSO, and pyridine are all appropriate solvents for this reaction while CH\textsubscript{2}Cl\textsubscript{2} failed to give any reaction even after several days at RT.

Method B:

A reaction vessel was charged with (1\textsuperscript{R},2\textsuperscript{R})-2-amino-1-phenylpropan-1-ol hydrochloride (2 g, 10.8 mmol), p-nitrophenyl acetate (1.76 g, 9.6 mmol) and HOBT (cat). Pyridine was added (16 mL) and the reaction mixture stirred 48 h at RT. Solvents were then removed under reduced pressure and the resulting crude syrup was chromatographed using 10% MeOH in CH\textsubscript{2}Cl\textsubscript{2}. Pure product was obtained in 81% yield (1.5 g, 7.8 mmol).

\begin{align*}
\text{\textsuperscript{1}H NMR (CDCl}_3\text{): } & \delta 7.33 - 7.19 (m, 5 H), 5.68 (d, 1 H, J = 8.6 \text{ Hz}), 4.58 (d, 1 H, J = 5.8 \text{ Hz}), 4.22 - 4.11 (m, 1 H), 3.44 (s, 1 H), 1.94 (s, 3 H), 1.09 (d, 3 H, J = 6.8 \text{ Hz}); \\
\text{\textsuperscript{13}C NMR APT (CDCl}_3\text{): } & \delta 171.04 \text{ (quaternary, acetate), 141.75 (quaternary, aromatic), 127.96, 127.34, 126.16 (CH, aromatic), 76.71 (CHO), 51.33 (CHN), 22.78 (CH}_3\text{, acetate), 17.33 (CH}_3\text{); IR (Neat): 3633.2 - 3127 (OH and NH), 1650.1, 1551.9, 1453.0, 1373.4, 1292.2, 1199.5, 1151.0, 1113.3,}
\end{align*}
1046.1, 761.9, 781.3 cm\(^{-1}\); \([\alpha]\)\(_D\) = -27.1 ° (c = 1.4, CHCl\(_3\)).

\((2S,3S,4E)-2-\{N-(\text{Stearyl})\text{amino}-1-O-(\text{tert-butyl}dime\text{thyl}silyl})-4-\text{tridecen}-1,3\text{-diol}\) (27):

A solution of 11b (155 mg, 0.45 mmol, 1.1 eq), p-nitrophenyl stearate (160 mg, 0.40 mmol), and HOBT (cat) was stirred in 2 mL of pyridine for 4 days at RT. Solvent was removed under reduced pressure and the resulting crude product chromatographed via flash chromatography (25% EtOAc in petroleum ether). Pure product was obtained in 88% yield (212 mg, 0.35 mmol).

\(^1\)H NMR (CDCl\(_3\)): \(\delta\) 6.04 (d, 1 H, \(J = 7.9\) Hz), 5.68 (dt, 1 H, \(J = 7, 15.7\) Hz), 5.36 (dd, 1 H, \(J = 6, 15.5\) Hz), 4.40 - 4.32 (m, 1 H), 3.88 - 3.78 (m, 3 H), 2.16 (t, 2 H, \(J = 7.5\) Hz), 2.05 - 1.93 (m, 2 H), 1.65 - 1.55 (m, 2 H), 1.21 (bs, 41 H), 0.9 - 0.8 (m, 15 H), 0.03 (s, 3 H), 0.02 (s, 3 H); \(^{13}\)C NMR APT (CDCl\(_3\)): \(\delta\) 173.51 (quaternary, amide), 133.22, 128.84 (CH, vinyl), 73.27 (CHO), 64.89 (CH\(_2\)O), 53.42 (CHN), 36.83, 32.28, 31.89, 29.65, 29.46, 29.35, 29.24, 29.13, 25.81 (CH\(_2\)), 25.74 (CH\(_3\), tBu), 22.64 (CH\(_2\)), 18.07 (quaternary, tBu), 14.07 (CH\(_3\)), -5.64 (SiCH\(_3\)); IR (Neat): 3522.2 - 3133.3, 2924.2, 2853.8, 1634.6, 1464.2, 1255.8, 1112.3, 966.7, 837.5, 776.9 cm\(^{-1}\); \([\alpha]\)\(_D\) = +5.4 ° (c = 1.2, CHCl\(_3\)).
5.19 Mitsunobu Inversion of N-Acyl β-Amino Alcohols (22 and 29)

(1S,2R)-2-[N-(Acetyl)amino]-1-O-pivaloyl-1-phenylpropan-1-ol (22):

To a stirred solution of 21 (29 mg, 0.15 mmol), Ph₃P (118 mg, 0.45 mmol) and pivalic acid (46 mg, 0.45 mmol) in THF (1 mL) was added DEAD (78 mg, 0.45 mmol). The reaction mixture was allowed to stir under argon at RT for 20 h. Solvents were removed under reduced pressure and the pure product isolated via flash chromatography using 80% EtOAc in petroleum ether as eluent (32 mg, 0.12 mmol, 80%). Note: Product is very weakly UV and ninhydrin active and is best visualized for TLC (Rf = 0.7 in 80% EtOAc/petroleum ether) using I₂ as visualizing agent.

¹H NMR (CDCl₃): δ 7.3 - 7.15 (m, 5 H), 5.74 (d, 1 H, J = 3.7 Hz), 5.46 (d, 1 H, J = 8.8 Hz), 4.38 - 4.36 (m, 1 H), 1.86 (s, 3 H), 1.20 (s, 9 H), 1.1 (d, 3 H, J = 6.8 Hz); ¹³C NMR APT (CDCl₃): δ 177.42, 169.22 (quaternary, acetate and pivalate), 137.34 (quaternary, aromatic), 128.32, 127.90, 126.19 (CH, aromatic), 77.06 (CHO), 48.86 (CHN), 38.95 (quaternary, tBu), 27.10 (CH₃, pivalate), 23.22 (CH₃, acetate), 15.20 (CH₃); IR (Neat): 3288.1, 1732.1, 1650.3, 1548.0, 1495.5, 1480.1, 1453.9, 1370.7, 1282.4, 1154.3, 1032.0, 973.2, 752.7, 701.6, 530.4 cm⁻¹; [α]D = +68.1° (c = 1.9, CHCl₃).

(2S,3R,4E)-2-[N-(Stearyl)amino]-1-O-[tert-butyldimethylsilyl]-3-O-pivaloyl-4-tridecen-1,3-diol (29):

A solution of 27 (96 mg, 0.16 mmol), Ph₃P (84 mg, 0.32 mmol) and pivalic acid (33 mg, 0.32 mmol) in THF (2 mL) was stirred under argon as DEAD (56 mg, 0.32 mmol) was added via syringe. After stirring 36 h at RT, solvents were removed under reduced pressure. The resulting syrup was chromatographed via flash chromatography (10% EtOAc in petroleum ether) to yield 75 mg pure product (0.11 mmol, 69%);
$^1$H NMR (CDCl$_3$): $\delta$ 5.72 (dt, 1 H, $J = 7$, 15.4 Hz), 5.62 (d, 1 H, $J = 9.1$ Hz), 5.38 (dd, 1 H, $J = 7.3$, 15.4 Hz), 5.24 (t, 1 H, $J = 7.7$ Hz), 4.27 - 4.15 (m, 1 H), 3.70 (dd, 1 H, $J = 2.8$, 10.2 Hz), 3.60 (dd, 1 H, $J = 4.0$, 10.2 Hz), 2.12 (t, 2 H, $J = 7.6$ Hz), 2.09 - 1.93 (m, 2 H), 1.67 - 1.51 (m, 2 H), 1.22 (bs, 4 H), 1.15 (s, 9 H), 0.87 - 0.80 (m, 15 H), 0.01 (s, 6 H); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 176.89, 172.36 (quaternary, pivalate and amide), 136.64, 125.23 (CH, vinyl), 72.73 (CHO), 61.55 (CH$_2$O), 51.83 (CHN), 37.04 (quaternary, pivalate tBu), 32.25, 31.87, 29.65, 29.48, 29.41, 29.33, 29.26, 29.10, 28.98 (CH$_2$), 27.04 (CH$_3$, pivalate), 25.81 (CH$_3$, tBuSi), 22.66 (CH$_2$), 18.19 (quaternary, tBuSi), 14.08 (CH$_3$), -5.52, -5.60 (SiCH$_3$); $[\alpha]_D^\circ = -3.2^\circ$ (c = 1.7, CHCl$_3$).
5.20 O-Acylation Without Inversion (23 and 28)

\((1R,2R)-2-[N-(Acetyl)amino]-1-O-pivaloyl-1-phenylpropan-1-ol (23)\):

A flame dried reaction flask was charged with compound 21 (101 mg, 0.52 mmol), DMAP (cat), and 2 mL of freshly distilled pyridine. Pivaloyl chloride (64 mg, 0.53 mmol) was then added dropwise via syringe. The reaction mixture was heated at 70 °C for 36 h. Solvents were removed under reduced pressure and the crude product purified via flash chromatography (70 mg, 0.25 mmol, 49%).

\(^1\)H NMR (CDCl\(_3\)): \(\delta 7.4 - 7.3 (m, 5 H), 5.65 (d, 1 H, J = 7.7 Hz), 5.49 (d, 1 H, J = 9.1 Hz), 4.53 - 4.43 (m, 1 H), 1.94 (s, 3 H), 1.22 (s, 9 H), 1.03 (d, 3 H, J = 6.8 Hz).

\((2S,3S,4E)-2-[N-(Stearyl)amino]-1-O-(tert-butyldimethylsilyl)-3-O-(pivaloyl)-4-tridecen-1,3-diol (28)\):

To a stirred solution of 27 (78 mg, 1.3 x 10\(^{-1}\) mmol) in dry pyridine (1 mL) was added DMAP (cat) and pivaloyl chloride (30 µL, 0.24 mmol, 1.8 eq). The reaction mixture was heated at 60 °C overnight under argon. Pyridine was removed under reduced pressure and the resulting crude product chromographed directly via flash chromatography (15% EtOAc in hexane) to yield 83 mg of pure product (0.12 mmol, 92%).

\(^1\)H NMR (CDCl\(_3\)): \(\delta 5.81 - 5.70 (m, 2 H), 5.45 - 5.35 (m, 2 H), 4.15 - 4.05 (m, 1 H), 3.67 (dd, 1 H, J = 2.7, 10.2 Hz), 3.53 (dd, 1 H, J = 4.5, 10.2 Hz), 2.12 (t, 2 H, J = 7.6 Hz), 2.04 - 1.96 (m, 2 H), 1.66 - 1.55 (m, 2 H), 1.23 (bs, 40 H), 1.15 (s, 9 H), 0.87 - 0.83 (m, 15 H), 0.00 (s, 6 H); \(^{13}\)C NMR APT (CDCl\(_3\)): \(\delta 177.78, 172.48 (quaternary, pivalate and amide), 136.81, 125.05 (CH, vinyl), 73.06 (CHO), 61.97 (CH\(_2\)O), 53.04 (CHN), 36.90 (quaternary, tBu), 32.24, 31.85,
29.64, 29.42, 29.36, 29.30, 29.24, 29.04, 28.83 (CH₂), 27.07 (CH₃, tBu), 25.77 (CH₃, tBuSi), 25.66, 22.61 (CH₂), 18.12 (quaternary, tBuSi), 14.05 (CH₃), -5.58, -5.66 (SiCH₃); [α]_D = + 14.7 ° (c = 3.6, CHCl₃).
5.21 Conversion of 28 and 29 to C_{13:1} Erythro- and Threo-Ceramides (30 and 31)

\((2S, 3R, 4E)-2-[\text{N-(Stearyl)amino]}-4\text{-tridecen-1,3-diol} \quad (30)\):  

A solution of 29 (51 mg, 0.073 mmol) and anhydrous NaOMe (20 mg, 0.37 mmol, 5 eq) in dry methanol was heated at 55 °C for 26 h. Solvents were evaporated and the crude product purified via flash chromatography (22 mg, 0.045 mmol, 62%). The chromatography eluent was 30% acetone in CH_{2}Cl_{2}.

\(^{1}\text{H NMR (CDCl}_3\)): \(\delta \ 6.26 \ (d, \ 1 \ H, \ J = 7 \ Hz), \ 5.79 \ (dt, \ 1 \ H, \ J = 7, 15.4 \ Hz), \ 5.53 \ (dd, \ 1 \ H, \ J = 6.6, 15.4 \ Hz), \ 4.36 - 4.28 \ (m, \ 1 \ H), \ 4.00 - 3.85 \ (m, \ 2 \ H), \ 3.71 \ (m, \ 1 \ H), \ 2.23 \ (t, \ 2 \ H, \ J = 7.5 \ Hz), \ 2.3 - 2.1 \ (bs, \ 2 \ H), \ 2.11 - 2.00 \ (m, \ 2 \ H), \ 1.72 - 1.57 \ (m, \ 2 \ H), \ 1.25 \ (bs, \ 40 \ H), \ 0.88 \ (\text{apparent t, 6 H, J = 6.6 Hz}); [\alpha]_D = -3.2 ^{\circ} \ (c = 1, \ CHCl_3)\).

\((2S, 3S, 4E)-2-[\text{N-(Stearyl)amino]}-4\text{-tridecen-1,3-diol} \quad (31)\):  

A solution of 28 (26 mg, 0.037 mmol) and anhydrous NaOMe (10 mg, 0.19 mmol, 5 eq) in dry methanol was heated at 55 °C for 26 h. Solvents were evaporated and the crude product purified via flash chromatography (11 mg, 0.022 mmol, 60%). The chromatography eluent was 30% acetone in CH_{2}Cl_{2}.

\(^{1}\text{H NMR (CDCl}_3\)): \(\delta \ 6.12 \ (d, \ 1 \ H, \ J = 7.3 \ Hz), \ 5.75 \ (ddt, \ 1 \ H, \ J = 1, 7, 15.4 \ Hz), \ 5.47 \ (ddt, \ 1 \ H, \ J = 1, 6.6, 15.4 \ Hz), \ 4.41 - 4.39 \ (m, \ 1 \ H), \ 4.00 - 3.87 \ (m, \ 1 \ H), \ 3.85 - 3.80 \ (m, \ 2 \ H), \ 2.23 \ (t, \ 2 \ H, \ J = 8 \ Hz), \ 2.10 - 1.97 \ (m, \ 2 \ H), \ 1.7 - 1.5 \ (m, \ 4 \ H), \ 1.25 \ (bs, \ 40 \ H), \ 0.88 \ (\text{apparent t, 6 H, J = 6.6 Hz}); [\alpha]_D = -8.5 ^{\circ} \ (c = 0.4, \ CHCl_3)\).
5.22 Synthesis of 3-O-Benzoyl and 3-O-Pivaloyl *Threeo*-Sphingosine Derivatives (32a,b and 35a,b)

**Benzoylation:**

**Method A** (From isolated TBDMS-protected Schiff base sphingosine):

A flame dried reaction vessel was charged with 177 mg (0.39 mmol) of compound 11d and 0.4 mL of dry pyridine. A catalytic amount of DMAP was added, followed by approximately 50 μL of benzoyl chloride. The resulting mixture was stirred under argon at RT for 16 h. Pyridine was removed using a rotary evaporator and the resulting residue applied directly to a silica gel column. Pure product was isolated in 69% yield (148 mg, 0.27 mmol) after eluting with 10% EtOAc in petroleum ether.

**Method B** (From crude TBDMS-protected Schiff base sphingosine):

Approximately 1 mmol of compound 1d was subjected to the DIBAL: Triisobutylaluminum (1:1) protocol to form the free 3-OH sphingosine derivative. Crude product from this reaction was azeotropically dried by rotary evaporating with 3 X 10 mL benzene. The crude oil thus dried was dissolved in 4 mL dry pyridine and stirred under argon. DMAP (cat) and benzoyl chloride (500 μL) were then sequentially added. After stirring for 16 h at RT under argon, pyridine was removed under reduced pressure. The crude product was applied directly to a silica gel column and eluted with 10% EtOAc in petroleum ether.
(2S,3S,4E)-2-[N-(Di phenylmethylene)amino]-3-O-benzoyl-1-O-(tert-butyldimethylsilyl)-4-tridecen-1,3-diol (32a):

(Oil, 462 mg, 0.75 mmol, 75% from crude 11b, method B).

$^1$H NMR (CDCl$_3$): $\delta$ 8.1 - 8.05 (m, 2 H), 7.7 - 7.2 (m, 13 H), 5.87 (dt, 1 H, J = 6.7, 15.4 Hz), 5.75 - 5.70 (m, 1 H), 5.47 (dd, 1 H, J = 7.8, 15.4 Hz), 3.98 - 3.86 (m, 3 H), 2.09 - 2.01 (m, 2 H), 1.27 (bs, 12 H), 0.93 - 0.85 (m, 12 H ), 0.05 (s, 3 H), 0.00 (s, 3 H); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 169.57, 165.40 (quaternary, imine and ester), 140.22, 136.58 (quaternary, aromatic), 136.11, 132.61 (CH, vinyl), 130.75 (quaternary, aromatic), 129.73, 129.64, 128.64, 128.26, 128.14, 128.00, 127.81, 125.64 (CH, aromatic), 75.71 (CHO), 66.80 (CHN), 63.24 (CH$_2$O), 32.30, 31.82, 29.39, 29.16, 29.10, 28.83 (CH$_2$), 25.92 (CH$_3$, tBu), 22.62 (CH$_2$), 18.36 (quaternary, tBu), 14.07 (CH$_3$), -5.31, -5.43 (CH$_3$Si); $[\alpha]_D$ = -21.3 ° (c = 3.4, CHCl$_3$); IR (Neat): 1721.7, 1627.6, 1463.2, 1448.0, 1360.9, 1260.4, 1106.5, 1026.3, 950.2, 836.6, 778.6, 696.1 cm$^{-1}$.

(2S,3S,4E)-2-[N-(Di phenylmethylene)amino]-3-O-benzoyl-1-O-(tert-butyldimethylsilyl)-4-nonen-1,3-diol (32b):

(Oil, 148 mg, 0.267 mmol, 69% from isolated 11d, method A).

$^1$H NMR (CDCl$_3$): $\delta$ 8.05 - 7.95 (m, 2 H), 7.6 - 7.15 (m, 13 H), 5.80 (dt, 1 H, J = 6.7, 15.4 Hz), 5.70 - 5.60 (m, 1 H), 5.4 (dd, 1 H, J = 7.8, 15.4 Hz), 3.9 - 3.75 (m, 3 H), 2.05 - 1.95 (m, 2 H), 1.4 - 1.2 (m, 4 H), 0.95 - 0.80 (m, 12 H ), -0.02 (s, 3 H), -0.07 (s, 3 H); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 169.63, 165.43 (quaternary, imine and ester), 140.26 (quaternary, aromatic), 136.60 (quaternary, aromatic), 136.06, 132.64 (CH, vinyl), 129.75, 129.68, 128.67, 128.28, 128.17, 128.02, 127.85, 125.65 (CH, aromatic), 75.75 (CHO), 66.82 (CHN), 64.25 (CH$_2$O), 32.00, 30.98 (CH$_2$), 25.92 (CH$_3$, tBu), 22.16 (CH$_2$), 18.39 (quaternary, tBu), 13.87 (CH$_3$), -5.31, -5.42 (CH$_3$Si); IR (Neat): 2927.7,
2865.3, 1721.3, 1269.1, 1106.9, 1069.5, 836.3, 779.4, 696.0 cm$^{-1}$.

Pivaloylation:

An example is provided below. Compound 35a was synthesized in similar fashion.

(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-1-O-(tert-butyldimethylsilyl)-3-O-pivaloyl-4-tridecen-1,3-diol (35b):

To a stirred solution of 11b (507 mg, 1.0 mmol) in pyridine (4 mL) was added pivaloyl chloride (4 mmol, 4 eq) and DMAP (cat). The resulting solution was heated at 50 °C for 14 h. The reaction was then quenched by pouring onto saturated NaHCO$_3$. The product was extracted with EtOAc and dried over K$_2$CO$_3$. After solvents were evaporated, pure product was isolated in 75% yield via flash chromatography (435 mg, 0.75 mmol, 75%).

$^1$H NMR (CDCl$_3$): $\delta$ 7.63 - 7.55 (m, 2 H), 7.45 - 7.35 (m, 2 H), 7.35 - 7.2 (m, 6 H), 5.76 (dt, 1 H, J = 6.8, 15 Hz), 5.48 - 5.31 (m, 2 H), 3.88 - 3.74 (m, 3 H), 2.07 - 1.95 (m, 2 H), 1.28 (bs, 12 H), 1.19 (m, 9 H), 0.89 (m, 12 H), 0.05 (s, 3 H), 0.00 (s, 3 H); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 177.19 (quaternary, pivalate), 168.95 (quaternary, imine), 140.28, 136.55 (quaternary, aromatic), 135.58, 129.67 (CH, vinyl), 128.69, 128.64, 128.56, 128.20, 127.96, 127.79, 126.05 (CH, aromatic), 74.69 (CHO), 66.60 (CHN), 64.42 (CH$_2$O), 38.77 (quaternary, tBu), 32.27, 31.86, 29.65, 29.47, 29.40, 29.22, 29.04, 28.89 (CH$_2$), 27.19, 25.92 (CH$_3$, tBu), 22.63 (CH$_2$), 14.06 (CH$_3$), -5.32, -5.44 (SiCH$_3$); IR (Neat): 1729.9, 1627.9, 1578.1, 1461.3, 1395.3, 1361.3, 1281.6, 1255.5, 1153.1, 1030.2, 1050.2, 969.1, 836.2, 779.3, 696.0 cm$^{-1}$, [$\alpha$]$_D$ = $+1.9^\circ$ (c = 1, CHCl$_3$).
(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-1-O-(tert-butyldimethylsilyl)-3-O-pivaloyl-4-octadecen-1,3-diol (35a):

(Oil, 925 mg, 1.4 mmol, 70% yield; chromatography eluent: 5% EtOAc in petroleum ether)

$^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ 7.7 - 7.6 (m, 2 H), 7.5 - 7.3 (m, 8 H), 5.76 (dt, 1 H, $J = 6.8$, 15 Hz), 5.48 - 5.31 (m, 2 H), 3.88 - 3.74 (m, 3 H), 2.10 - 2.00 (m, 2 H), 1.30 (bs, 22 H), 1.20 (bs, 9 H), 0.88 (m, 12 H), 0.05 (s, 3 H), 0.00 (s, 3 H);

$^{13}$C NMR APT (CDCl$_3$): $\delta$ 177.01 (quaternary, pivalate), 168.90 (quaternary, imine), 140.17, 136.46 (quaternary, aromatic), 135.48, 132.23 (CH, vinyl), 129.90, 129.62, 128.58, 128.14, 127.90, 127.70, 126.02 (CH, aromatic), 74.59 (CHO), 66.53 (CHN), 64.35 (CH$_2$O), 38.69 (quaternary, pivalate tBu), 32.21, 31.82, 29.57, 29.48, 29.39, 29.24, 28.95, 28.83 (CH$_2$), 27.13, 25.86 (CH$_3$), 22.57 (CH$_2$), 18.31 (quaternary, tBuSi), 14.01 (CH$_3$), -5.39, -5.51 (SiCH$_3$); IR (Neat): 1730.6, 1628.0, 1462.3, 1280.4, 1255.3, 1154.2, 1115.8, 969.1, 836.3, 779.2, 695.8 cm$^{-1}$, $[\alpha]_D^\circ = +2.4$° (c = 1.2, CHCl$_3$).
5.23 Cleavage of the TBDMS-Protection to Provide Glycosyl Acceptors (33a,b and 36a,b)

An example is provided below. All other desilylations were performed in a similar fashion. Yields and chromatography eluents are listed in parentheses.

\[(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-3-O-pivaloyl-4-tridecen-1,3-diol \ (36b)\):

To a stirred solution of 35b (422 mg, 0.73 mmol) in 1 mL dry THF was added 1.1 eq TBAF (800 μL of 1.0 M TBAF in THF). The resulting solution was stirred 2 h at RT. The solvents were passed through a plug of silica gel and evaporated under reduced pressure. Pure product was isolated after flash chromatography in 74% yield (259 mg, 0.54 mmol).

\[^1\text{H}\text{ NMR (CDCl}_3\text{)}: \delta 7.65 - 7.55 (m, 2 H), 7.5 - 7.4 (m, 2 H), 7.4 - 7.2 (m, 6 H), 5.77 (dt, 1 H, J = 6.8, 15 Hz), 5.48 - 5.29 (m, 2 H), 3.80 (t, 1 H, J = 7.7 Hz), 3.69 (bs, 1 H), 3.60 (t, 1 H, J = 7.6 Hz), 3.54 - 3.48 (m, 1 H), 2.04 - 1.96 (m, 2 H), 1.24 (bs, 12 H), 1.20 (bs, 6 H), 1.16 (s, 3 H), 0.88 (t, 3 H, J = 6.6 Hz) ; \]^\text{13C NMR APT (CDCl}_3\text{)}: \delta 170.48 (quaternary, pivalate), 143.84, 143.66 (quaternary, aromatic), 137.05 (CH, vinyl), 136.16 (CH, aromatic), 128.52, 128.34, 128.23, 128.14, 127.99, 127.64, 127.40, 126.52, 125.79, 125.55, 124.82 (CH, aromatic), 100.12 (quaternary, oxazolidine), 74.68, 73.89 (CHO), 66.56 (CH\text{}_2\text{O}), 66.38 (CHN), 63.44 (CH\text{}_2\text{O}), 61.47 (CHN), 38.97 (quaternary, pivalate tBu), 32.19, 31.83, 29.33, 29.21, 28.95, 28.86, 28.74 (CH\text{}_2\text{)}, 27.22, 27.10 (CH\text{}_3\text{)}, 22.63 (CH\text{}_2\text{)}, 14.04 (CH\text{}_3\text{}); [\alpha]_D = + 2.4 ^\circ \ (c = 1.2, \text{CHCl}_3) \}; \text{Note oxazolidine tautomerism.}
(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-3-O-pivaloyl-4-octadecen-1,3-diol (36a):

(Oil, 431 mg, 0.74 mmol, 74% yield, chromatography eluent: 10% EtOAc in petroleum ether)

$^1$H NMR (CDCl$_3$): $\delta$ 7.65 - 7.55 (m, 2 H), 7.55 - 7.45 (m, 2 H), 7.4 - 7.2 (m, 6 H), 5.76 (dt, 1 H, $J$ = 6.8, 15 Hz), 5.47 - 5.29 (m, 2 H), 3.80 (t, 1 H, $J$ = 7.7 Hz), 3.70 (bs, 1 H), 3.60 (t, 1 H, $J$ = 7.5 Hz), 3.54 - 3.48 (m, 1 H), 2.04 - 1.96 (m, 2 H), 1.25 (bs, 22 H), 1.20 (bs, 6 H), 1.16 (s, 3 H), 0.88 (t, 3 H, $J$ = 6.6 Hz); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 170.45 (quaternary, pivalate), 143.82, 143.58, 139.73 (quaternary, aromatic), 136.93 (CH, vinyl), 136.26 (quaternary, aromatic), 136.05, 132.25 (CH, vinyl), 130.11, 129.96, 128.70, 128.43, 128.22, 128.06, 127.90, 127.55, 127.34, 126.46, 127.73, 125.55, 124.82 (CH, aromatic), 100.06 (quaternary, oxazolidine), 74.65, 73.86 (CHO), 66.50 (CH$_2$O), 66.33 (CHN), 63.30 (CH$_2$O), 61.45 (CHN), 38.80 (quaternary, pivalate tBu), 32.24, 32.14, 31.86, 29.60, 29.51, 29.39, 29.33, 29.28, 29.00, 28.90 (CH$_2$), 27.16, 27.04 (CH$_3$), 22.63 (CH$_2$), 14.04 (CH$_3$); $[\alpha]_D$ = - 37.5° (c = 1.3, CHCl$_3$).

(2S,3S,4E)-2-[N-(Diphenylmethylene)amino]-1-O-benzoyl-4-tridecen-1,3-diol (33a):

(Oil, 212 mg, 0.427 mmol, 62% yield; chromatography eluent: 15% EtOAc in petroleum ether).

$^1$H NMR (CDCl$_3$): $\delta$ 8.0 - 7.95 (m, 2 H), 7.8 - 7.2 (m, 13 H), 5.76 (dt, 1 H, $J$ = 6.7, 15.2 Hz), 5.42 (dd, 1 H, $J$ = 8.0, 15.2 Hz), 4.43 (dd, 1 H, $J$ = 5.4, 11.5 Hz), 4.31 (dd, 1 H, $J$ = 5.1, 11.5 Hz), 4.24 (t, 1 H, 8 Hz), 3.43 - 3.41 (m, 1 H), 2.92 - 2.88 (bs, 1 H), 2.07 - 1.95 (m, 2 H), 1.40 - 1.15 (m, 12 H), 0.88 (t, 3 H, $J$ = 7 Hz); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 166.10 (quaternary, benzoate), 144.81, 144.66 (quaternary, aromatic), 135.58, 132.99 (CH, vinyl), 129.55, 128.29, 128.23,
128.14, 128.05, 127.52, 127.35, 126.02 (CH, aromatic), 99.41 (quaternary, oxazolidine), 81.50, 72.83 (CHO), 65.45, 63.88 (CH$_2$O), 64.86, 62.83 (CHN), 32.16, 31.78, 29.30, 29.15, 28.84, 22.58 (CH$_2$), 14.04 (CH$_3$); (Note the Schiff base-oxazolidine tautomerism); IR (Neat): 1723.8, 1601.7, 1490.1, 1451.3, 1271.0, 1110.5, 1026.8, 968.5, 751.4, 704.1, 629.7; [$\alpha$]$_D$ = + 13.3° (c = 0.63, CHCl$_3$).

(2$S$,3$S$,4E)-2-[N-(Diphenylmethylene)amino]-1-O-benzoyl-4-nonen-1,3-diol (33b):

(Oil, 25 mg, 0.06 mmol, 63% yield, 10% EtOAc in petroleum ether).

$^1$H NMR (CDCl$_3$): $\delta$ 8.0 - 7.9 (m, 2 H), 7.7 - 7.2 (m, 13 H), 5.74 (dt, 1 H, J = 6.7, 15.2 Hz), 5.41 (dd, 1 H, J = 8.1, 15.2 Hz), 4.41 (dd, 1 H, J = 5.2, 11.5 Hz), 4.36 - 4.20 (m, 2 H), 3.44 - 3.37 (m, 1 H), 3.0 - 2.7 (bs, 1 H), 2.05 - 1.95 (m, 2 H), 1.4 - 1.1 (m, 4 H), 0.90 (t, 3 H, J = 7 Hz); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 166.25 (quaternary, benzoate), 144.87, 144.72 (quaternary, aromatic), 135.67, 133.10 (CH, vinyl), 132.94, 130.88, 129.79, 129.64, 128.81, 128.37, 128.29, 128.23, 128.11, 127.61, 127.43, 126.08 (CH, aromatic), 99.47 (oxazolidine), 81.56 (CHO), 63.94 (CH$_2$O), 62.89 (CHN), 31.89, 31.04, 22.21 (CH$_2$), 13.89 (CH$_3$); IR (Neat): 1723.9, 1601.0, 1490.1, 1451.0, 1379.9, 1272.1, 1176.1, 1113.4, 1069.8, 1026.3, 968.7, 751.4, 704.2, 629.8, 532.3 cm$^{-1}$; [$\alpha$]$_D$ = + 14.5° (c = 1.1, CHCl$_3$).
5.24 Detection of Acyl Migration (34 and 35b)

Benzoates:

\[(2S,3S,4E)-2-[N-(\text{Di phenylmethylen})\text{amino}]\text{-1-O-benzoyl-3-O-(tert-butyl}dime\text{thylisilyl)}\text{-4-tridecen-1,3-diol (34).}\]

Compound 33a (123 mg, 0.25 mmol) was dissolved in 1 mL dry DMF. TBDMSI (74 mg, 0.5 mmol, 2 eq) and imidazole (50 mg, 0.73 mmol, 2.9 eq) were then added. The mixture was stirred at RT 48 h before pouring onto EtOAc and extracting with two volumes of 0.1% NaHCO₃ and two volumes of saturated NaHCO₃. The organic layer was dried over K₂CO₃, filtered and evaporated. Pure product was obtained in 97% yield (147 mg, 0.241 mmol). Analysis of the \(^1\text{H}, ^{13}\text{C},\) and IR spectra clearly showed that migration had occurred (i.e. none of the spectra were identical to those of 32a).

\(^1\text{H NMR (CDCl}_3\):} \ \delta \ 8.1 - 8.0 (m, 2 H), 7.75 - 7.65 (m, 2 H), 7.65 - 7.3 (m, 11 H), 5.82 (dt, 1 H, \(J = 6.3, 15.4\) Hz), 5.70 (dd, 1 H, \(J = 8.9, 15.4\) Hz), 4.62 (dd, 1 H, \(J = 3.50, 11\) Hz), 4.54 (dd, 1 H, \(J = 8.2, 11\) Hz), 4.38 (t, 1 H, \(J = 6.5\) Hz), 4.03 - 3.96 (m, 1 H), 2.19 - 2.11 (m, 2 H), 1.37 (bs, 12 H), 1.06 - 0.93 (m, 12 H), 0.10 (s, 3 H), 0.00 (s, 3 H); \(^{13}\text{C NMR APT (CDCl}_3\):} \ \delta \ 169.07, 166.31 (quaternary, benzoate and imine), 140.14, 136.55 (quaternary, aromatic), 133.02, 132.64 (CH, vinyl), 130.46 (quaternary, aromatic), 129.81, 129.76, 129.52, 128.63, 128.49, 128.19, 128.14, 128.08, 127.82 (CH, aromatic), 75.06 (CHO), 66.18 (CH₂O), 66.03 (CHN), 32.27, 31.83, 29.42, 29.24, 29.19 (CH₂), 25.83 (CH₃, tBu), 22.65 (CH₂), 18.13 (quaternary, tBu), 14.04 (CH₃), -4.65 (Si-CH₃); IR (Neat): 1724.2, 1627.0, 1602.5, 1490.2, 1448.8, 1378.6, 1380.5, 1314.3, 1272.7, 1176.0, 1094.5, 1069.5, 970.8, 835.7 cm\(^{-1}\); \([\alpha]_D = +16.4^\circ\) (c =1, CHCl₃).
Pivalates

Desilylated 36b was resilylated via the following procedure:

Compound 36b (69 mg, 0.145 mmol) was dissolved in 1 mL dry DMF. TBDMSI (45 mg, 0.30 mmol) and imidazole (30 mg, 0.44 mmol) were then added. The mixture was stirred at RT 20 h before pouring onto EtOAc and extracting with two volumes 0.1% NaHCO₃ and two volumes of NaHCO₃ (sat'd). The organic layer was dried over K₂CO₃, filtered and evaporated. Pure product was obtained in 92% yield (77 mg, 0.133 mmol) and had a §H NMR spectrum identical to that of 35b.
5.25 β-Selective Glycosylation (37a-c and 38a-d):

The general procedure for glycosylation is illustrated by the example given below. All other glycosylations were carried out in similar fashion.

To a stirred solution of 33a (206 mg, 0.41 mmol), freshly prepared (2,3,4-tri-O-acetyl-β-D-xylopyranosyl) bromide (209 mg, 0.616 mmol, 1.5 eq), and flame dried powdered 4 Å molecular sieves (400 mg) in ten mL CH₂Cl₂ under argon, was added silver triflate (158 mg, 0.616 mmol, 1.5 eq) in portions as a solid over approximately 20 min. The resulting mixture was protected from light and allowed to stir at room temperature overnight. Silver salts were then removed by filtering through a pad of Celite. Solvents were removed under reduced pressure and the crude oil was subjected to flash chromatography (30% EtOAc in petroleum ether). Pure product, 38a, was obtained in 56% isolated yield (173 mg, 0.229 mmol). Solvents used for chromatography and isolated yields are listed in parentheses.

O-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→1')-(2S,3S,4E)-2-[N-(diphenylmethylene)amino]-3-O-pivaloyl-4-octadecen-1,3-diol (37a):
(Amorphous white solid, 432 mg, 0.37 mmol, 72% yield; chromatography eluent: 40% EtOAc in petroleum ether).

¹H NMR (CDCl₃, 500 MHz): δ 7.65 - 7.55 (m, 2 H), 7.45 - 7.15 (m, 8 H), 5.68 (dt, 1 H, J = 7, 15.4 Hz), 5.37 (t, 1 H, J = 6.8 Hz), 5.31 (d, 1 H, J = 3.6 Hz), 5.26 (dd, 1 H, J = 7.4, 15.4 Hz), 5.13 (t, 1 H, J = 8.8 Hz), 5.07 (dd, 1 H, J = 8.0, 10.4 Hz), 4.90 (dd, 1 H, J = 3.6, 10.2 Hz), 4.87 (dd, 1 H, J = 7.2, 8.5 Hz), 4.55 (d, 1 H,
J = 7.3 Hz), 4.35 - 4.31 (m, 2 H), 4.06 (dd, 2 H, J = 1.6, 6.9 Hz), 4.0 (dd, 1 H, J = 5, 12 Hz), 3.94 (dd, 1 H, J = 7.2, 9.6 Hz), 3.79 - 3.74 (m, 3 H), 3.64 (dd, 1 H, J = 4.3, 9.8 Hz), 3.52 - 3.49 (m, 1 H, J = 6.9 Hz), 3.07 - 3.01 (m, 1 H, J = 7.7 Hz), 2.17 - 1.96 (m, 23 H, contains seven singlets at 2.14, 2.08, 2.038, 2.020, 2.015, and 1.96 ppm), 1.25 (bs, 22 H), 1.16 (s, 9 H), 0.88 (t, 3 H, J = 7 Hz); ¹H NMR (CDCl₃, 250 MHz): δ 7.65 - 7.55 (m, 2 H), 7.45 - 7.15 (m, 8 H), 5.68 (dt, 1 H, J = 6.9, 15 Hz), 5.40 - 5.21 (m, 3 H), 5.13 (t, 1 H, J = 8.8 Hz), 5.06 (dd, 1 H, J = 7.8, 10.4 Hz), 4.88 (dd, 1 H, J = 3.3, 10.6 Hz), 4.87 (t, 1 H, J = 8 Hz), 4.54 (d, 1 H, J = 7.2 Hz), 4.34 (dd, 1 H, J = 2, 12.3 Hz), 4.32 (d, 1 H, J = 7.7 Hz), 4.07 (d, 1 H, J = 7 Hz), 4.03 - 3.91 (m, J = 3 H), 3.82 - 3.73 (m, 3 H), 3.64 (dd, 1 H, J = 4.4, 9.5 Hz), 3.53 - 3.48 (m, 1 H), 2.14 - 1.96 (m, 23 H, contains six singlets at 2.14, 2.08, 2.04, 2.023, 2.020, 1.96 ppm), 1.24 (bs, 22 H), 1.16 (s, 9 H), 0.88 (t, 3 H, J = 6.4 Hz); ¹³C NMR APT (CDCl₃): δ 176.72, 169.95, 169.78, 169.63, 169.38, 169.10, 168.70 (esters and imine), 139.54, 135.99 (quaternary aromatic), 135.53, 129.88 (CH, vinyl), 128.37, 128.12, 127.99, 127.75, 125.22 (CH, aromatic), 100.79, 99.71 (anomeric), 75.94, 73.87, 73.00, 72.12, 71.60, 70.62, 70.24 (CHO), 69.44 (CH₂O), 68.76, 66.39, 54.30 (CHX), 61.91 (CH₂O), 60.57 (CH₂O), 38.51 (quaternary, tBu), 31.98, 31.59, 29.33, 28.74, 28.74, 28.55 (CH₂), 26.90 (CH₃), 22.36 (CH₂), 20.51, 20.39, 20.26, 20.16, 13.81 (CH₃); [α]D = +24.6° (c = 0.4, CHCl₃).
O-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→1')-(2S,3S,4E)-2-[N-(diphenylmethylene)amino]-3-O-pivaloyl-4-tridecen-1,3-diol (37b):

(Amorphous white solid, 433 mg, 0.40 mmol, 71% yield; chromatography eluent: 50% EtOAc in petroleum ether).

$^1$H NMR (CDCl$_3$, 500 MHz): δ 7.7 - 7.55 (m, 2 H), 7.45 - 7.1 (m, 8 H), 5.68 (dt, 1 H, J = 7, 15.4 Hz), 5.37 (t, 1 H, J = 7 Hz), 5.30 (d, 1 H, J = 3.5 Hz), 5.26 (dd, 1 H, J = 7.8, 15.4 Hz), 5.13 (t, 1 H, J = 8.8 Hz), 5.07 (dd, 1 H, J = 8, 10.4 Hz), 4.90 (dd, 1 H, J = 3.5, 10.4 Hz), 4.88 (dd, 1 H, J = 1.6, 7.2 Hz), 4.55 (d, 1 H, J = 7.4 Hz), 4.35 - 4.31 (m, 2 H), 4.07 - 4.05 (m, 2 H), 4.01 (dd, 1 H, J = 5.0, 11.8 Hz), 3.94 (apparent t, 1 H, J = 8 Hz), 3.80 - 3.74 (m, 3 H), 3.64 (dd, 1 H, J = 4.2, 9.8 Hz), 3.52 - 3.49 (m, 1 H), 2.14 - 1.96 (m, 23 H, contains seven singlets at 2.14, 2.09, 2.04, 2.039, 2.024, 2.018 and 1.96 ppm), 1.22 (bs, 12 H), 1.16 (s, 9 H), 0.87 (t, 3 H, J = 7 Hz); $^1$H NMR (CDCl$_3$, 250 MHz): δ 7.65 - 7.55 (m, 2 H), 7.45 - 7.1 (m, 8 H), 5.69 (dt, 1 H, J = 6.9, 15 Hz), 5.40 - 5.24 (m, 3 H), 5.13 (t, 1 H, J = 8.8 Hz), 5.07 (dd, 1 H, J = 7.8, 10.4 Hz), 4.88 (dd, 1 H, J = 3.3, 10.6 Hz), 4.88 (t, 1 H, J = 8 Hz), 4.55 (d, 1 H, J = 7.3 Hz), 4.34 (dd, 1 H, J = 1.6, 12 Hz), 4.32 (d, 1 H, J = 7.8 Hz), 4.06 (d, 1 H, J = 6.9 Hz), 4.03 - 3.73 (m, 3 H), 3.8 - 3.7 (m, 3 H), 3.64 (dd, 1 H, J = 4.1, 9.4 Hz), 3.50 (dd, 1 H, J = 2.8, 9.8 Hz), 2.2 - 1.93 (m, 23 H, contains six singlets at 2.14, 2.09, 2.04, 2.024, 2.020, 1.96 ppm), 1.22 (bs, 12 H), 1.16 (s, 9 H), 0.87 (t, 3 H, J = 6.6 Hz); $^{13}$C NMR APT (CDCl$_3$): δ 176.93, 170.12, 169.95, 169.84, 169.54, 169.25, 168.87 (esters and imine), 139.67, 136.11 (quaternary aromatic), 135.73 (CH, vinyl), 129.99, 128.49, 128.23, 128.12, 127.87, 125.29 (CH, aromatic), 100.96, 99.86 (anomeric), 76.06, 74.03, 73.09, 72.21, 71.71, 70.75, 70.36 (CHO), 69.62 (CH$_2$O), 68.85,
O-(2,3,4,6-Tetra-O-acetyl-D-glucopyranosyl)-(1→1')-
(2S,3S,4E)-2-[N-(diphenylmethylene)amino]-3-O-pivaloyl-4-
tridecen-1,3-diol (37c):

(Amorphous white solid, 244 mg, 0.302 mmol, 69% yield, chromatography eluent: 30% EtOAc in petroleum ether).

\(^1\)H NMR (CDCl\(_3\), 250 MHz): \(\delta 7.65 - 7.55\) (m, 2 H), 7.5 - 7.4 (m, 2 H), 7.4 - 7.15 (m, 6 H), 5.67 (dt, 1 H, \(J = 6.8\), 15.4 Hz), 5.43 - 5.38 (m, 1 H), 5.27 (dd, 1 H, \(J = 7.4\), 15.4 Hz), 5.16 (t, 1 H, \(J = 9.5\) Hz), 5.04 (t, 1 H, \(J = 9.5\) Hz), 4.98 (dd, 1 H, \(J = 7.8\), 9.5 Hz), 4.57 (d, 1 H, \(J = 7.8\) Hz), 4.15 (dd, 1 H, \(J = 4.5\), 12.2 Hz), 3.99 - 3.90 (m, 2 H), 3.76 - 3.70 (m, 2 H), 3.54 (ddd, 1 H, \(J = 2.6\), 4.4, 9.9 Hz), 2.10 - 1.93 (m, 14 H contains three acetate singlets at 2.04, 2.02, and 1.99 ppm), 1.22 (m, 12 H), 1.16 (s, 9 H), 0.87 (t, 3 H, \(J = 6.8\) Hz); \(^{13}\)C NMR APT (CDCl\(_3\)): \(\delta 177.04\) (quaternary, pivalate), 170.48, 170.16, 169.46, 169.40 (quaternary, esters and imine), 139.75, 136.26 (quaternary aromatic), 135.75, 130.02 (CH, vinyl), 128.55, 128.31, 128.23, 128.11, 127.90, 125.37 (CH, aromatic), 100.70 (anomeric), 74.06, 72.97, 71.65, 71.21 (CHO), 70.11 (CH\(_2\)O), 68.24, 64.70 (CHX), 61.72 (CH\(_2\)O), 38.74 (quaternary, tBu), 32.22, 31.77, 29.30, 29.13, 29.00, 28.80 (CH\(_2\)), 27.13 (CH\(_3\), tBu), 22.55 (CH\(_2\)), 20.59, 20.51 (CH\(_3\)), 14.01 (CH\(_3\)); IR (Neat): 1752.0, 1364.2, 1220.0, 1153.0, 1037.2, 699.5 cm\(^{-1}\); \([\alpha]_D^0 = +1.7\) ° (c = 0.5, CHCl\(_3\)).
O-(2,3,4-Tri-O-acetyl-β-D-xylopyranosyl)-(1→3)-(2S,3S,4E)-2-
[N-(diphenylmethylene)amino]-1-O-benzoyl-4-tridecen-1,3-diol
(38a):

(Oil, 173 mg, 0.229 mmol, 56% yield; chromatography eluent: 30% EtOAc in
petroleum ether)

$^1$H NMR (CDCl$_3$): $\delta$ 8.0 - 7.9 (m, 2 H), 7.65 - 7.5 (m, 3 H), 7.45 - 7.25 (m, 8
H), 7.2 - 7.1 (m, 2 H), 5.76 (dt, 1 H, $J = 6.7$, 15.4 Hz), 5.49 (dd, 1 H, $J = 8.1$,
15.4 Hz), 5.08 (apparent t, 1 H, $J = 8.6$ Hz) 4.99 - 4.90 (m, 2 H), 4.50 (d, 1 H, $J$
= 6.8 Hz), 4.39 - 4.32 (m, 2 H), 4.28 (t, 1 H, $J = 8$ Hz), 4.05 (dd, 1 H, $J = 5.2$,
11.8 Hz), 3.98 - 3.91 (m, 1 H), 3.24 (dd, 1 H, $J = 9.0$, 11.7 Hz), 2.10 - 2.0 (m, 2
H), 2.03 (s, 3 H), 1.97 (s, 3 H), 1.45 (s, 3 H), 1.40 - 1.20 (m, 12 H), 0.88 (t, 3
H, $J = 7$ Hz); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 170.20, 169.96, 169.75, 169.26, 166.11
(quaternary, esters and imine), 139.91, 136.29 (quaternary, aromatic), 135.70,
132.79 (CH, vinyl), 130.11 (quaternary, aromatic), 129.93, 129.50, 128.79,
128.33, 128.26, 128.19, 128.15, 127.82, 127.38 (CH, aromatic), 100.27 (CH,
anomeric), 83.26, 71.72, 70.68, 68.98 (CHO), 65.63 (CH$_2$O), 63.98 (CHN),
61.95 (CH$_2$O), 32.22, 31.79, 29.37, 29.16, 29.10, 28.98, 22.58 (CH$_2$), 20.67,
20.58, 19.78 (CH$_3$, acetate), 14.03 (CH$_3$); $[\alpha]_D = -29.6^\circ$ (c = 0.72, CHCl$_3$); MS
(CI-ammonia): 756 (M+1), 292 bp.
O-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-(1→3)-(2S,3S,4E)-2-[N-(diphenylmethyleneamino]-1-O-benzoyl-4-tridecen-1,3-diol (38b):

(Oil, 269 mg, 0.325 mmol, 63% yield, chromatography eluent: 30% EtOAc in petroleum ether)

$^1$H NMR (CDCl$_3$): δ 8.0 - 7.9 (m, 2 H), 7.6 - 7.5 (m, 3 H), 7.4 - 7.2 (m, 8 H), 7.2 - 7.1 (m, 2 H), 5.77 (dt, 1 H, J = 6.6, 15.4 Hz), 5.54 (dd, 1 H, J = 8.7, 15.4 Hz), 5.17 - 5.03 (m 3 H), 4.49 (d, 1 H, J = 7.4 Hz), 4.40 - 4.21 (m, 4 H), 4.15 - 3.99 (m, 2 H), 3.61 - 3.56 (m, 1 H), 2.10 - 2.0 (m, 2 H), 2.09 (s, 3 H), 2.01 (s, 3 H), 1.94 (s, 3 H), 1.38 (s, 3 H), 1.24 (bs, 12 H), 0.86 (t, 3 H, J = 7 Hz); $^{13}$C NMR APT (CDCl$_3$): δ 170.49, 170.22, 170.07, 169.28, 169.22, 165.98 (quaternary, esters and imine), 139.96, 136.26 (quaternary, aromatic), 135.90, 132.76 (CH, vinyl), 130.05 (quaternary, aromatic), 129.87, 129.45, 128.76, 128.32, 128.13, 127.75, 127.34 (CH, aromatic), 100.06 (CH, anomeric), 84.68, 73.03, 71.50, 70.91, 68.26 (CHO), 65.52 (CH$_2$O), 63.62 (CHN), 62.00 (CH$_2$O) 32.24, 31.72, 29.30, 29.19, 29.10, 28.95, 22.51 (CH$_2$), 20.63, 20.43, 19.63 (CH$_3$, acetates), 13.99 (CH$_3$); [α]$_D$ = -12.5° (c = 0.8, CHCl$_3$).

O-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→3)-(2S,3S,4E)-2-[N-(diphenylmethyleneamino]-1-O-benzoyl-4-tridecen-1,3-diol (38c):

(Amorphous white solid, 284 mg, 1.26 mmol, 71% yield; chromatography eluent: 50% EtOAc in petroleum ether)

$^1$H NMR (CDCl$_3$): δ 7.95 - 7.85 (m, 2 H), 7.55 - 7.45 (m, 3 H), 7.4 - 7.2 (m, 8 H), 7.15 - 7.05 (m, 2 H), 5.69 (dt, 1 H, J = 6.4, 15.4 Hz), 5.45 (dd, 1 H, J = 8.5, 15.4 Hz), 5.28 (d, 1 H, J = 3.3 Hz), 5.10 - 5.00 (m, 2 H), 4.94 - 4.84 (m, 2 H),
$4.41$ (d, 1 H, J = 7.9 Hz), $4.40$ (d, 1 H, J = 7.8 Hz), $4.36$ - $4.25$ (m, 3 H), $4.21$ (t, 1 H, J = 8 Hz), $4.10$ - $3.96$ (m, 3 H), $3.93$ - $3.85$ (m, 1 H), $3.85$ - $3.70$ (m, 2 H), $3.46$ - $3.41$ (m, 1 H), $2.15$ - $1.91$ (m, 20 H, contains six acetate singlets at 2.08, 2.06, 2.04, 1.99, 1.98, and 1.91 ppm), $1.37$ (s, 3 H), 1.3 - 1.1 (m, 12 H), 0.83 (t, 3 H, J = 7 Hz); $^{13}$C NMR APT (CDCl$_3$): δ 170.16, 170.04, 169.98, 169.90, 169.57, 169.51, 168.92, 165.98 (quaternary, esters and imine), 140.00, 136.25 (quaternary, aromatic), 135.87, 132.74 (CH, vinyl), 130.05 (quaternary, aromatic), 129.90, 129.43, 128.71, 128.26, 128.14, 128.08, 127.76, 127.20 (CH, aromatic), 101.03, 99.79 (CH, anomeric), 84.26, 76.27, 73.09, 72.31, 71.38, 70.85, 70.49, 68.97, 66.47 (CHO), 65.51 (CH$_2$O), 63.68 (CHN), 62.20, 60.65 (CH$_2$O), 32.27, 31.71, 29.27, 29.16, 29.07, 28.98, 22.48 (CH$_2$), 20.72, 20.60, 20.48, 20.36, 19.73 (CH$_3$, acetate), 13.95 (CH$_3$); IR (CHCl$_3$): 2926.7, 1753.7, 1447.0, 1369.1, 1231.2, 1056.4, 703.5 cm$^{-1}$; $[\alpha]$D = -16.4° (c = 0.8, CHCl$_3$).

O-(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-O-(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→3)-(2S,3S,4E)-2-[N-(diphenylmethylene)amino]-1-O-benzoyl-4-nonen-1,3-diol (38d):

(Amorphous white solid, 79 mg, 0.074 mmol, 60% yield; chromatography eluent: 50% EtOAc in petroleum ether)

$^1$H NMR (CDCl$_3$, 250 MHz): δ 8.0 - 7.9 (m, 2 H), 7.6 - 7.5 (m, 3 H), 7.4 - 7.2 (m, 8 H), 7.17 - 7.10 (m, 2 H), 5.74 (dt, 1 H, J = 6.5, 15.4 Hz), 5.51 (dd, 1 H, J = 8.8, 15.4 Hz), 5.33 (d, 1 H, J = 3.4 Hz), 5.14 - 5.06 (m, 2 H), 4.96 - 4.90 (m, 2 H), 4.47 (d, 1 H, J = 7.9 Hz), 4.45 (d, 1 H, J = 7.8 Hz), 4.42 - 4.23 (m, 4 H), 4.16 - 4.06 (m, 3 H), 3.98 - 3.90 (m, 1 H), 3.88 - 3.75 (m, 2 H), 3.53 - 3.44 (m, 1 H), 2.10 - 2.0 (m, 2 H), 2.14 (s, 3 H), 2.12 (s, 3 H), 2.05 (s, 3 H), 2.04
(s, 3 H), 1.97 (s, 3 H), 1.96 (s, 3 H), 1.41 (s, 3 H), 1.35 - 1.20 (m, 4 H), 0.88
(t, 3 H, J = 7 Hz); COSY (CDCl₃): δ 8.0 - 7.1 (aromatic), 5.74 (Ha), 5.51 (Hb),
5.33 (H₄'), 5.14 - 5.06 (H₂', H₃), 4.96 - 4.90 (H₂, H₃'), 4.47 (H₁), 4.45 (H₁'),
4.42 - 4.23 (Hc, He, Hf, H₆), 4.16 - 4.06 (H₆, H₆', H₆'), 3.98 - 3.90 (Hd), 3.88
- 3.75 (H₅', H₄), 3.53 - 3.44 (H₅); ¹³C NMR APT (CDCl₃): δ 170.25, 170.16,
170.07, 169.99, 169.60, 169.01, 166.10 (quaternary, esters and imine), 139.93,
136.35 (quaternary, aromatic), 135.91, 132.81 (CH, vinyl), 130.84 (quaternary,
aromatic), 129.97, 129.49, 128.78, 128.34, 128.20, 128.14, 127.84, 127.31
(CH, aromatic), 101.09, 99.85 (CH, anomeric), 84.38, 76.30, 73.15, 72.38,
71.44, 70.91, 70.56, 69.03, 66.50 (CHO), 65.59 (CH₂O), 63.74 (CHN), 62.23,
60.70 (CH₂O), 31.98, 31.13, 22.22 (CH₂), 20.80, 20.67, 20.56, 20.42, 19.80
(CH₃, acetate), 13.83 (CH₃); IR (KBr): 1747.3, 1627.2, 1450.6, 1365.8,
1231.5, 1054.9, 701.7, 602.8 cm⁻¹; [α]D = - 19.1° (c = 0.6, CHCl₃).
5.26 Synthesis of β-Lactosyl-\textit{Three}-Ceramide (39 - 41a,b)

\textbf{Hydrolysis of Schiff base protecting groups:}

The general procedure for quantitative cleavage of the Schiff base is shown in the example provided below.

To a stirred solution of 38b (100 mg, 0.09 mmol) in 2 mL of THF : CH$_2$Cl$_2$ (1:1) were added 200 μL CF$_3$CO$_2$H and 5 drops H$_2$O. The reaction mixture was allowed to stir at RT until TLC indicated cleavage was complete (4 h). The reaction was quenched by pouring onto NaHCO$_3$ (sat'd). The aqueous layer was extracted with several volumes of CH$_2$Cl$_2$. Combined organic layers were dried over K$_2$CO$_3$ and evaporated under reduced pressure. Pure product (39b) was isolated in quantitative yield (86 mg, 0.09 mmol) via flash chromatography (90% EtOAc in hexanes as eluent).

O-\{(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-O-\{(2,3,6-tri-O-acetyl-β-D-glucopyranosyl)-(1→1')-(2S,3S,4E)-2-amino-3-O-pivaloyl-4-tridecen-1,3-diol \quad (39b):

(Oil, 86 mg, 0.092 mmol, 100% yield; chromatography eluent: 90% EtOAc in hexanes)

\begin{verbatim}
$^1$H NMR (CDCl$_3$, 500 MHz): δ 5.72 (dt, 1 H, J = 7.3, 15.4 Hz), 5.40 (ddt, 1 H, J = 1.4, 7, 15.4 Hz), 5.34 (dd, 1 H, J = 1, 3.4 Hz), 5.20 - 5.14 (m, 2 H, contains t at 5.19 ppm, J = 9.3 Hz), 5.10 (dd, 1 H, J = 7.9, 10.4 Hz), 4.95 (dd, 1 H, J = 3.5, 10.4 Hz), 4.89 (dd, 1 H, J = 7.9, 9.6 Hz), 4.50 - 4.47 (m, 2H, contains doublet at 4.48 ppm, J = 8 Hz), 4.45 (d, 1 H, J = 8 Hz), 4.13 (dd, 1 H, J = 6.3, 11.1 Hz), 4.08 (dd, 1 H, J = 7, 11.3 Hz), 4.08 (dd, 1 H, J = 5, 12 Hz), 3.87 (t, 1 H, J = 7.3 Hz), 3.80 (t, 1 H, J = 9.5 Hz), 3.74 (dd, 1 H, J = 6.3, 9.6 Hz), 3.59 (ddd, 1 H, J = 2, 5, 10 Hz), 3.47 (dd, 1 H, J = 5.4, 9.6 Hz), 3.01 - 2.98 (m, 1 H), 2.17 - 1.96 (m, 25 H, contains six acetate singlets at 2.15, 2.12, 2.06, 2.043, 2.042, and 1.96
\end{verbatim}
NMR: $^{1}H$ NMR (CDCl$_3$, 250 MHz): $\delta$ 5.72 (dt, 1 H, $J = 7, 15.4$ Hz), 5.45 - 5.34 (m, 2 H), 5.23 - 5.07 (m, 3 H), 4.98 - 4.86 (m, 2 H), 4.51 - 4.44 (m, 3 H), 4.20 - 4.00 (m, 3 H), 3.90 - 3.71 (m, 3 H), 3.64 - 3.55 (m, 1 H), 3.46 (dd, 1 H, $J = 5.4, 9.2$ Hz), 3.02 - 2.96 (m, 1 H), 2.20 - 1.93 (m, 25 H, contains six singlets at 2.15, 2.12, 2.063, 2.061, 2.04 and 1.97 ppm), 1.25 (bs, 12 H), 1.21 (bs, 9 H), 0.88 (t, 3 H, $J = 6.4$ Hz); $^{13}C$ NMR APT(CDC$_3$): $\delta$ 170.25, 170.24, 170.04, 169.95, 169.66, 168.95 (quaternary, esters), 135.73, 125.13 (CH, vinyl), 100.99, 100.52 (CH, anomeric), 76.13, 74.50, 72.68, 72.57, 71.49, 71.23, 70.90, 70.61, 69.03, 66.53 (CHO), 61.88, 60.73 (CH$_2$O), 54.00 (CHN), 38.89 (quaternary, tBu), 31.77, 29.59, 29.30, 29.18, 29.01, 28.83 (CH$_2$), 27.10 (CH$_3$, tBu), 22.57 (CH$_2$), 20.74, 20.54, 20.42, 14.01 (CH$_3$); $[\alpha]_D^0 = -4.5$° (c = 3.5, CHCl$_3$).

**N-Acylation (40a and b):**

The general procedure for acylation of the amino group is given below. To a stirred solution of azeotropically dried 38b (86 mg, 0.09 mmol) and DMAP (cat) in 1 mL pyridine (dried over CaH$_2$) was added palmityl chloride (32 mg, 0.12 mmol, 1.3 eq). The reaction mixture was allowed to stir for 12 h at RT (TLC revealed complete consumption of starting material after 12 h). The reaction was quenched by pouring onto Et$_2$O/NaHCO$_3$ (std). The aqueous layer was separated and the organic layer was washed with brine. After drying (K$_2$CO$_3$) the solvents were removed via rotary evaporation. Crude product was purified via flash chromatography (50% EtOAc in hexanes) to yield 86 mg of pure 40b (0.07 mmol, 80%).
O-(2,3,4,6-Tetra-O-acetyl-ß-D-galactopyranosyl)-(1→4)-O-
(2,3,6-tri-O-acetyl-ß-D-glucopyranosyl)-(1→1)-(2S,3S,4E)-2-
[N-(hexadecanoyl)amino]-3-O-pivaloyl-4-octadecen-1,3-diol (40a):
(Oil, 94 mg, 0.076 mmol, 88% yield, chromatography eluent: 50% EtOAC in hexanes)

$^1$H NMR (CDCl$_3$, 250 MHz): $\delta$ 5.75 - 5.64 (m, 2 H, contains doublet at 5.66 ppm, J = 9.5 Hz), 5.39 - 5.32 (m, 3 H), 5.18 (t, 1 H, J = 9.5 Hz), 5.11 (dd, 1 H, J = 8, 11 Hz), 4.95 (dd, 1 H, J = 3.3, 10.6 Hz), 4.88 (dd, 1 H, J = 7.7, 9.9 Hz), 4.48 - 4.40 (m, 3 H, contains two doublets: $\delta$ 4.47, J = 7.7 Hz, and $\delta$ 4.41, J = 8 Hz), 4.28 - 4.23 (m, 1 H), 4.15 - 4.05 (m, 3 H), 3.90 - 3.63 (m, 3 H), 3.60 - 3.54 (m, 1 H), 3.45 (dd, 1 H, J = 6, 10 Hz), 2.18 - 1.97 (m, 25 H, contains five singlets at 2.16, 2.13, 2.07, 2.05 and 1.97 ppm), 1.7 - 1.5 (m, 2 H), 1.25 (bs, 46 H), 1.19 (bs, 9 H), 0.88 (apparent triplet, 6 H, J = 7 Hz); $^{13}$C NMR APT (CDCl$_3$): $\delta$ 177.27, 172.60, 170.22, 170.07, 169.99, 169.64, 168.98 (quaternary, esters and amide), 136.34, 124.43 (CH, vinyl), 100.99, 100.61 (anomeric), 76.00, 72.52, 72.44, 71.55, 70.88, 70.58, 70.56, 68.95 (CHO), 68.16 (CH$_2$O), 66.50 (CHO), 61.79, 60.71 (CH$_2$O), 51.29 (CHN), 38.80 (quaternary, tBu), 36.68, 32.16, 31.83, 29.59, 29.42, 29.36, 29.27, 29.04, 28.75 (CH$_2$), 27.04 (CH$_3$), 25.54, 22.60 (CH$_2$), 20.72, 20.59, 20.55, 20.42 (CH$_3$), 14.01 (CH$_3$); IR (Neat): 1753.8, 1665.5, 1465.6, 1369.3, 1232.1, 1155.5, 1057.7 cm$^{-1}$; [$\alpha$]$_D$ = -1.6° (c = 3, CHCl$_3$).

O-(2,3,4,6-Tetra-O-acetyl-ß-D-galactopyranosyl)-(1→4)-O-
(2,3,6-tri-O-acetyl-ß-D-glucopyranosyl)-(1→1')-(2S,3S,4E)-2-
[N-(hexadecanoyl)amino]-3-O-pivaloyl-4-tridecen-1,3-diol (40b):
(Oil, 86 mg, 0.073 mmol, 80% yield; chromatography eluent: 50% EtOAc in hexanes)

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ 5.72 (dt, 1 H, J = 7, 14.2 Hz), 5.65 (d, 1 H, J = 9.1 Hz), 5.38 - 5.33 (m, 3 H), 5.18 (t, 1 H, J = 9.3 Hz), 5.10 (dd, 1 H, J = 7.9, 10.4 Hz), 4.95 (dd, 1 H, J = 3.4, 10.4 Hz), 4.88 (dd, 1 H, J = 8, 9.5 Hz), 4.48 - 4.44
(m, 2 H, contains doublet at 4.47 ppm, \( J = 7.8 \) Hz), 4.41 (d, 1 H, \( J = 7.9 \) Hz), 4.29 - 4.24 (m, 1 H), 4.13 (dd, 1 H, \( J = 6.4, 11.2 \) Hz), 4.10 - 4.06 (m, 2 H, contains dd at 4.09 ppm, \( J = 7.2, 9.8 \) Hz), 3.88 - 3.85 (m, 2 H), 3.78 (t, 1 H, \( J = 9.4 \) Hz), 3.57 (ddd, 1 H, \( J = 2, 4.9, 9.8 \) Hz), 3.45 (dd, 1 H, \( J = 5.8, 10 \) Hz), 2.19 - 1.96 (m, 25 H, contains seven singlets at 2.15, 2.12, 2.07, 2.05, 2.04, and 1.96 ppm), 1.7 - 1.5 (m, 2 H), 1.25 (bs, 36 H), 1.21 (bs, 9 H), 0.88 (apparent t, 6 H, \( J = 6 \) Hz); \(^1\)H NMR (CDCl\(_3\), 250 MHz): \( \delta \) 5.76 - 5.63 (m, 2 H, contains doublet at 5.65 ppm, \( J = 9 \) Hz), 5.40 - 5.33 (m, 3 H), 5.22 - 5.10 (m, 2 H), 4.95 (dd, 1 H, \( J = 3.3, 10.6 \) Hz), 4.86 (apparent t, 1 H, \( J = 10 \) Hz), 4.49 - 4.40 (m, 3 H), 4.28 - 4.23 (m, 1 H), 4.15 - 4.05 (m, 3 H), 3.90 - 3.75 (m, 3 H), 3.60 - 3.54 (m, 1 H), 3.5 (dd, 1 H, \( J = 5.3, 10 \) Hz), 2.15 - 1.96 (m, 25 H, contains five singlets at 2.15, 2.12, 2.07, 2.05 and 1.97 ppm), 1.7 - 1.5 (m, 2 H), 1.25 (bs, 36 H), 1.21 (bs, 9 H), 0.88 (t, 6 H, \( J = 6.4 \) Hz); \(^{13}\)C NMR APT (CDCl\(_3\)): \( \delta \) 177.28, 172.54, 170.22, 170.16, 170.01, 169.92, 169.60, 168.96 (quaternary, esters and amide), 136.34, 124.49 (CH, vinyl), 100.98, 100.62 (anomeric), 76.00, 72.54, 72.44, 71.58, 70.88, 70.60, 68.98 (CHO), 68.16 (CH\(_2\)O ), 66.53 (CHO), 61.80, 60.72 (CH\(_2\)O), 51.31 (CHN), 38.80 (quaternary, tBu), 36.66, 32.14, 31.80, 29.55, 29.39, 29.25, 29.17, 28.98, 28.74 (CH\(_2\)), 27.04 (CH\(_3\)), 25.53, 22.56 (CH\(_2\)), 20.69, 20.52, 20.39 (CH\(_3\)), 14.01 (CH\(_3\)); \([\alpha]_D = -2.3^\circ \) (c = 2.6, CHCl\(_3\)).

**Zemplen Deacetylation (41a,b):**

The general procedure for Zemplen deacetylation is provided below.

To a stirred solution of 40b (68 mg, 5.8 x 10\(^{-2}\) mmol) in anhydrous MeOH (1 mL) was added NaOMe (8.5 mg, 0.16 mmol, 2.7 eq). The resulting solution was refluxed at 50 °C for 19 h. Crude product was chromatographed via flash chromatography (30% MeOH in CH\(_2\)Cl\(_2\)) to yield 30.4 mg of pure 41b (3.8 x 10\(^{-2}\) mmol, 66%).
O-(β-D-Galactopyranosyl)-(1→4)-O-(β-D-glucopyranosyl)-(1→1')-(2S,3S,4E)-2-[N-(hexadecanoyl)amino]-4-tridecen-1,3-diol (41a):

(White amorphous solid, 32 mg, 0.049 mmol, 78% yield, chromatography eluent: 25% MeOH in CH₂Cl₂).

¹H NMR (d₆-DMSO : D₂O (98:2), 500 MHz): δ 5.59 (dt, 1 H, J = 7, 15.4 Hz), 5.34 (dd, 1 H, J = 5.4, 15.4 Hz), 4.20 - 4.17 (m, 3 H), 3.89 - 3.87 (m, 1 H), 3.72 (d, 1 H, J = 11 Hz), 3.62 - 3.56 (m, 3 H), 3.53 - 3.43 (m, 5 H), 3.35 - 3.26 (m, 4 H), 3.0 (t, 1 H, J = 8 Hz), 2.10 (dt, 1 H, J = 7, 14 Hz), 2.0 (dt, 1 H, J = 7, 14 Hz), 1.94 - 1.92 (m, 2 H), 1.47 - 1.39 (m, 2 H), 1.34 - 1.0 (bs, 46 H), 0.83 (apparent t, 6 H, J = 7 Hz); ¹H NMR (d₆-DMSO : D₂O (98:2), 250 MHz): δ 5.59 (dt, 1 H, J = 7, 15.4 Hz), 5.34 (dd, 1 H, J = 5.4, 15.4 Hz), 4.20 - 4.17 (m, 3 H), 3.88 - 3.86 (m, 1 H), 3.72 (d, 1 H, J = 11.7 Hz), 3.62 - 3.36 (m, 8 H), 3.33 - 3.23 (m, 4 H), 3.05 - 2.95 (m, 1 H), 2.13 - 2.01 (m, 2 H), 2.01 - 1.89 (m, 2 H), 1.55 - 1.39 (m, 2 H), 1.34 - 1.18 (bs, 46 H), 0.83 (t, 6 H, J = 6.4 Hz); MS (Cl): 862 (M +1), 264 (bp); [α]D = - 23.4° (c = 0.24, pyridine).

O-(β-D-Galactopyranosyl)-(1→4)-O-(β-D-glucopyranosyl)-(1→1')-(2S,3S,4E)-2-[N-(hexadecanoyl)amino]-4-tridecen-1,3-diol (41b):

(White amorphous solid, 31 mg, 0.039 mmol, 67% yield, chromatography eluent: 30% MeOH in CH₂Cl₂).

¹H NMR (d₆-DMSO : D₂O (98:2), 500 MHz): δ 5.55 (dt, 1 H, J = 7, 15.4 Hz), 5.34 (dd, 1 H, J = 5.6, 15.4 Hz), 4.20 - 4.17 (m, 3 H), 3.89 - 3.87 (m, 1 H), 3.72 (d, 1 H, J = 10.5 Hz), 3.62 - 3.56 (m, 3 H), 3.53 - 3.43 (m, 5 H), 3.35 - 3.26 (m, 4 H), 3.0 (t, 1 H, J = 8.3 Hz), 2.10 (dt, 1 H, J = 7, 14 Hz), 2.01 (dt, 1 H, J = 7, 14 Hz), 1.94 - 1.91 (m, 2 H), 1.48 - 1.39 (m, 2 H), 1.34 - 1.0 (bs, 36 H), 0.83 (apparent t, 6 H, J = 7 Hz); ¹H NMR (d₆-DMSO : D₂O (98:2), 250 MHz): δ 5.55 (dt,
1 H, J = 7, 15.4 Hz), 5.34 (dd, 1 H, J = 5.3, 15.4 Hz), 4.25 - 4.14 (m, 3 H), 3.97 - 3.79 (m, 1 H), 3.72 (d, 1 H, J = 11.7 Hz), 3.63 - 3.36 (m, 8 H), 3.33 - 3.23 (m, 4 H), 3.05 - 2.95 (m, 1 H), 2.13 - 2.01 (m, 2 H), 2.01 - 1.88 (m, 2 H), 1.55 - 1.39 (m, 2 H), 1.34 - 1.18 (bs, 36 H), 0.83 (t, 6 H, J = 6.4 Hz); MS (Cl): 792 (M +1), 194 (bp); [α]D = -58.9° (c = 0.1, pyridine).
APPENDIX

SELECTED $^1$H AND $^{13}$C NMR SPECTRA
10b'}
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It appears to be a chemical structure diagram.
REFERENCES


22. Compound 1d was crystallized after careful purification and storing at -26 °C for approximately three weeks. Subsequent crystallization was accomplished more rapidly by adding a seed crystal. Compound 1d was quite hygroscopic and therefore required storing in a dessicator.


28. DIBAL was added as a 0.5 M solution in either THF or hexanes (see Experimental). Colors ranged from bright yellow to dark orange depending on the Schiff base used.


36. Observed m.p. for the free amino diol was 87 - 89 °C. Literature values were:

- a) 86 - 87 °C
- b) 88.0 - 88.5 °C

Observed $[\alpha]_D$ for 12c was $+8.2^\circ$ (c = 2.3, CHCl₃). Literature values were:

- a) $+8.43^\circ$ (CHCl₃)
- b) $+8.78^\circ$ (c = 1.2, CHCl₃)


60. Compound 3a was treated with 2 eq RCO2H, 2 eq Ph3P and 2 eq DEAD at both RT and reflux in the following solvents: THF, CH2Cl2, Et2O, hexanes and benzene.


