Chapter III

Phenolytic Kinetic Resolution of Benzyloxy Epoxides and Asymmetric Synthesis of D-erythro-Sphinganine via Co(III)(salen)-Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxides
SECTION I:
Co(III)(salen)-catalyzed PKR of two stereocentered benzyloxy epoxides

3.1.1 Introduction

Enantiomerically pure *anti*- or *syn*-1-aryloxy-3-benzyloxy-2-alcohols (1 and 2) are valuable ‘building blocks’ for asymmetric synthesis of bioactive pharmaceuticals.¹ These structural units are present in numerous bioactive compounds such as erythritol,² an antidiabetic C4 polyol, β-adrenolytic drugs,³ and broussonetine family of naturally-occurring iminosugars,⁴ which show potent glucosidase inhibitory activities with enormous therapeutic potential as *anti*-tumor and *anti*-HIV agents. In addition, these aryloxy benzyloxy alcohols (1a-f and 2) can be used as precursors of 1,2 diols and simple oxiranes, which are versatile intermediates in the synthesis of bioactive molecules (Fig. 1).

![Structures of anti- and syn-1-aryloxy-3-benzyloxy-2-alcohols (1 & 2) and Co(III)-salen complex (3)](image)

**Fig. 1:** Structures of *anti*- and *syn*-1-aryloxy-3-benzyloxy-2-alcohols (1 & 2) and Co(III)-salen complex (3)

The Jacobsen’s hydrolytic and phenolic kinetic resolutions (HKR & PKR) of terminal epoxides with one stereocenter, catalyzed by Co(III)-salen complex 3 employ water
and phenol as nucleophiles, respectively.\(^5\) While HKR of epoxides has been comprehensively studied in recent years to understand its mechanistic and synthetic aspects that includes a recent study\(^6\) relating to HKR of functionalized epoxides with two stereocentres, its phenolic version (PKR) has been less explored. In the present work, we have extended the scope of the applicable substrates to cover multifunctionalized epoxides with two stereocenters and employing functionalized phenols (5a-f and 5c) as the nucleophiles.

### 3.1.2 Review of literature

Literature search reveals that there are no reports available for the syntheses of enantiomerically pure anti- or syn-1-aryloxy-3-benzyloxy-2-alcohols.

### 3.1.3 Present Work

#### 3.1.3.1 Objective

The aim of such an investigation is to obtain enantioenriched 1-aryloxy-3-benzyloxy-2-alcohols (1 and 2) by a direct method from the respective racemic materials, thus complementing the other tedious routes.\(^7\) In this section we have described a flexible, novel method that employs PKR of racemic benzyloxy epoxides 4 and 6 to generate benzyloxy alcohols 1 and 2 respectively, with two stereocenters of high optical purities in a single step (Schemes 1 and 2).

### 3.1.4 Results and Discussion

We envisioned that the extension of PKR to the two- stereocentered racemic epoxides would enable us to obtain both the enantiomers of anti- or syn- aryloxy alcohols depending upon the chiral ligands chosen. Thus, the racemic anti- and syn-benzyloxy epoxides (4 and 6), the substrates for PKR, were efficiently prepared in a highly diastereoselective manner from the corresponding (Z)- and (E)- allylic alcohols respectively, by following a reported procedure.\(^6\) In this strategy, the relative
stereochemistry between the benzyloxy and epoxide groups is established prior to the PKR step itself and in this way a simple asymmetric reaction can be used to obtain the key enantiomerically pure 1-aryloxy-3-benzyloxy-2-alcohols (1 and 2).

Thus, when PKR of racemic anti-benzyloxy epoxide 4 was performed with (R, R)-Co(III)-salen complex 3 (0.044 equiv) and 4-acetylphenol (1 equiv) (5c) in tert-butyl methyl ether (TBME), the corresponding anti-1-aryloxy-3-benzyloxy-2-alcohol 1c was isolated in 98% yield and 86% ee (entry c, table 1). The PKR can be conducted at low temperatures (-20 °C), although yields obtained were found to be low. Further, the stereoselectivities in the PKR displayed strong epoxide concentration dependence, requiring at least 2.2 equivalents of epoxides to realize excellent enantioselectivity (Scheme 1).

![Scheme 1. PKR of anti-benzyloxy epoxides.](image)

A variety of phenolic substrates were then screened for the PKR process that led to the isolated yields of 1a-f, with complete regiocontrol. The benzyloxy epoxides underwent the reaction only with electron-deficient phenols (Table 1). Unfortunately, simple phenolic substrates like 1-naphthol and electron-rich phenols failed to undergo reaction.
Table 1. PKR of anti-benzyloxy epoxide<sup>a</sup>

<table>
<thead>
<tr>
<th>entry</th>
<th>phenols (R) (5a-f)</th>
<th>anti-benzyloxy alcohol (1a-f)</th>
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<tr>
<td></td>
<td>yield (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ee (%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>a</td>
<td>4-CN</td>
<td>87</td>
</tr>
<tr>
<td>b</td>
<td>4-NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>89</td>
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<tr>
<td>c</td>
<td>4-COCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>98</td>
</tr>
<tr>
<td>d</td>
<td>4-CHO</td>
<td>75</td>
</tr>
<tr>
<td>e</td>
<td>4-CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>81</td>
</tr>
<tr>
<td>f</td>
<td>2,3,5-Cl&lt;sub&gt;3&lt;/sub&gt;</td>
<td>78</td>
</tr>
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</table>

<sup>a</sup> racemic azido or benzyloxy epoxide 5 (5 mmol), (R,R)-Co(III)-salen complex 3 (86 mg, 0.1 mmol), TBME, 3 A° MS, or phenol (6) (2.25 mmol);<sup>b</sup> isolated yield after column chromatographic purification with respect to nucleophile;<sup>c</sup> ee determined by chiral HPLC analysis (see the experimental section for details).

Similarly, the racemic syn-benzyloxy epoxide 6, prepared readily from the corresponding cinnamyl alcohol,<sup>6</sup> was subjected to PKR under identical reaction condition that produced the corresponding enantiopure syn-product 2 in high isolated yield and ee (Scheme 2).

Scheme 2. PKR of syn-benzyloxy epoxides.

Interestingly, only electron-deficient phenols reacted efficiently with the syn-benzyloxy epoxides also, with good yields and ees. The formation of 1-aryloxy-3-
benzylxy-2-alcohols 1 and 2 was confirmed by $^1$H and $^{13}$C NMR and IR spectroscopy.

Fig. 2: $^1$H and $^{13}$C of 4-((2R,3S)-4-(tert-butyl dimethylsiloxy)-3-(benzylxy)-2-hydroxybutoxy)benzonitrile (1c)
Example 1: The $^1$H NMR spectrum of 1c showed typical signals in the aromatic region at $\delta$ 6.85-6.95 and at $\delta$ 7.89-7.95 for the aromatic protons. The disappearance of signals in the epoxide region at $\delta$ 2.70-3.06 confirmed the opening of epoxide with phenol (5c). Its $^{13}$C NMR spectrum showed two typical signals at $\delta$ 69.1 and 71.0 due to the methylenic (-CH$_2$O) and methinic (-CHO-) carbons respectively. A typical signal at $\delta$ 196.4 for the carbonyl carbon (-CO-) confirmed the opening of epoxide. The disappearance of signals at $\delta$ 45.4 and 50.9 in its $^{13}$C spectrum and an absorption band at 1671 cm$^{-1}$ in its IR spectrum further substantiated the opening of epoxide with 4-acetylphenol (Fig. 2).

Example 2: The $^1$H NMR spectrum of 2 showed typical signals in the aromatic region at $\delta$ 6.81-6.82 and at $\delta$ 7.85-7.90 for the protons of acetyl substituted phenolic part and signals at $\delta$ 6.85-7.37 for another two aromatic rings. The disappearance of signals in the epoxide region at $\delta$ 2.46-3.21 confirmed the opening of epoxide with phenol (5c). Its $^{13}$C NMR spectrum showed two typical signals at $\delta$ 26.2 for the acetyl
protons (-COCH$_3$) and other signals at 68.0, 70.8 and 81.4 due to the methinic (-CHOH), methylenic (-CH$_2$O-) and benzylic methine (-CHOH) carbons respectively. A typical signal at $\delta$ 196.2 for the carbonyl carbon (-CO-) confirmed the opening of epoxide. The formation of 2 was also substantiated by the presence of molecular ion peak at m/z 399.1567 in its HRMS spectrum (Fig. 3).

The relative and absolute stereochemistry of the products 1 and 2 were confirmed by the X-ray crystallographic analysis (see Fig. 4 for 1c).
3.1.4 Conclusion

In conclusion, the (salen) Co(III)-catalysed PKR of racemic benzyloxy epoxides provided a highly practical route to enantiopure anti- or syn-benzyloxy alcohols 1 and 2 in a single step. The reaction is convenient to carry out under mild conditions displaying a wide range of substrate scope. We believe that this PKR strategy will find applications in the field of asymmetric synthesis of bioactive molecules owing to the flexible nature of the synthesis of racemic benzyloxy epoxides and the readily accessible catalyst in both enantiomeric forms.

3.1.5. Experimental

General procedure for the phenolic kinetic resolutions of anti- and syn- aryloxy benzyloxy alcohols: (see Schemes 1 and 2)

To a stirred solution of (R, R)-(salen) Co[OC(CF$_3$)$_3$](H$_2$O) (3) (86 mg, 0.1 mmol), molecular sieve (100 mg, 3 Å) and racemic anti- or syn-benzyloxy epoxides (4 or 6) (5 mmol), in tert-butyl methyl ether (0.15 mL), phenol (2.25 mmol) (5a-f) was added at 25 °C. The reaction was stirred for 6-15 h till all the phenol gets converted (as monitored by TLC). Solvent was removed under reduced pressure. The crude product was purified by column chromatography over silica gel (eluting with pet.
ether/EtOAc) to give optically pure anti- or syn-1-aryloxy-3-benzyloxy-2-alcohols in
pure form. The enantiomeric purity was determined by chiral HPLC analysis.

(2R, 3S)-4-(4-(tert-Butyldimethylsiloxy)-3-(benzoyloxy)-2-
hydroxybutoxy)benzo-nitrile (1a)

**Yield:** 87%; colorless solid, mp: 62-63 °C; [α]D 25 -7.74 (c 1, CHCl3); IR (CHCl3, cm⁻¹): ʋ max 778, 835, 1096, 1172, 1258, 1302, 1454, 1508, 1605, 2224, 2856, 2883, 2929, 2953, 3474; ¹H NMR (200 MHz, CDCl3): δ 0.09 (s, 6H), 0.91 (s, 9H), 2.90-2.92 (m, 1H), 3.64 (q, J = 5.4 Hz, 1H), 3.86-3.89 (m, 2H), 4.10-4.18 (m, 3H), 4.51-4.73 (dd, J = 11.5 and 11.7 Hz, 2H), 6.90-6.96 (m, 2H), 7.27 (m, 5H), 7.53-7.61 (m, 2H); ¹³C NMR (50 Hz, CDCl3): -5.5, 18.1, 25.7, 62.9, 69.3, 70.6, 72.5, 78.2, 104.0, 115.1, 118.8, 127.7, 127.8, 128.2, 133.7, 137.7, 161.9; **Optical purity:** 98% ee determined by HPLC analysis (Chiral OD-H column, n-hexane/2-propanol (80:20), 0.5 mL/min, 210 nm) Retention time: t_major = 10.15 and t_minor = 11.35 min.; HRMS (ESI) m/z Calcd for C24H33NO4NaSi [M + Na]^+, 450.2071; found, 450.2070.

(2R, 3S)-4-(tert-Butyldimethylsiloxy)-1-(4-nitrophenoxy)-3-(benzoyloxy)butan-2-ol (1b)

**Yield:** 89%; colorless liquid; [α]D 25 -16.52 (c 1, CHCl3); IR (neat, cm⁻¹): ʋ max 752, 778, 1111, 1263, 1340, 1517, 1593, 2856, 2928, 3472; ¹H NMR (200 MHz, CDCl3): δ 0.10 (s, 6H), 0.92 (s, 9H), 2.97 (br s, 1H), 3.58-3.67 (m, 1H), 3.87-3.90 (m, 2H), 4.10-4.21 (m, 3H), 4.51-4.73 (dd, J = 11.6 and 11.8 Hz, 2H), 6.89-6.97 (m, 2H), 7.24-7.32 (m, 5H), 8.14-8.22 (m, 2H); ¹³C NMR (50 MHz, CDCl3): δ -5.4, 18.2, 25.8, 63.0, 69.8, 71.0, 72.6, 78.1, 114.4, 125.7, 127.9, 128.4, 137.7, 141.6, 163.7; **Optical purity:** 97% ee determined by HPLC analysis (Chiral OJ-H column, n-hexane/2-propanol (80:20), 0.5 mL/min, 210 nm) Retention time: t_major = 12.53 and t_minor = 15.12 min.; HRMS (ESI): m/z Calcd for C23H33NO6NaSi [M + Na]^+, 470.1969; found, 470.1975.
1-(4-((2R,3S)-4-(tert-butyldimethylsiloxy)-3-(benzoyloxy)-2-hydroxybutoxy)phenyl)ethanone (1c)

**Yield:** 98%; colorless solid; **mp:** 91-92 °C; [α]D^25^ -19.89 (c 1.0, CHCl₃); **IR** (CHCl₃, cm⁻¹): ν_max 699, 775, 957, 1093, 1258, 1359, 1470, 1575, 1600, 1671, 2856, 2928, 3473; **¹H NMR** (200 MHz, CDCl₃) δ 0.09 (s, 6H), 0.92 (s, 9H), 2.56 (s, 3H), 2.90 (br s 1H), 3.61-3.69 (m, 1H), 3.87-3.90 (dd, J = 3.0 and 5.4 Hz, 2H), 4.09-4.19 (m, 3H), 4.53-4.74 (dd, J = 11.6 Hz, 2H), 6.85-6.95 (m, 2H), 7.27 (s, 5H), 7.89-7.95 (m, 2H); **¹³C NMR** (50 MHz, CDCl₃): δ -5.43, 18.29, 25.91, 63.25, 69.19, 71.02, 72.79, 78.40, 114.25, 127.88, 127.99, 128.43, 130.56, 137.96, 162.62, 196.42; **Optical purity:** 86% ee determined by HPLC analysis (OJ-H column, n-hexane/2-propanol (80:20), 0.5 mL/min, 254 nm) Retention time: t_minor = 14.38 and t_major = 15.07 min.

**HRMS (ESI):** m/z Calcd for C_{25}H_{36}O_{5}NaSi [M + Na]^+, 467.2224; found, 467.2220

(2R, 3S)-4-(4-(tert-Butyldimethylsiloxy)-3-(benzoyloxy)-2-hydroxybutoxy)benzaldehyde (1d)

**Yield:** 75%; gum; [α]D^25^ +14.02 (c 1, CHCl₃); **IR** (neat, cm⁻¹): ν_max 755, 834, 1097, 1256, 1462, 1509, 1600, 1693, 2928, 3454; **¹H NMR** (200 MHz, CDCl₃): δ 0.09 (s, 6H), 0.92 (s, 9H), 2.95 (br s, 1H), 3.63-3.69 (m, 1H) 3.87-3.91 (m, 2H), 4.11-4.21 (m, 3H), 4.62 (dd, J = 11.6 and 11.8 Hz, 2H), 6.96-7.00 (m, 2H), 7.24-7.35 (m, 5H), 7.80-7.85 (m, 2H), 9.88 (s, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ -5.4, 18.2, 25.9, 63.2, 69.3, 71.0, 72.7, 78.3, 114.8, 128, 128.4, 130.1, 131.9, 137.9, 163.7, 190.4; **Optical purity:** 99% ee determined by HPLC analysis (OJ-H column, n-hexane/2-propanol (80:20), 0.5 mL/min, 254 nm) Retention time: t_minor = 14.38 and t_major = 15.07 min.; **HRMS (ESI):** m/z Calcd for C_{24}H_{36}O_{5}NaSi [M + Na]^+, 453.2068; found, 453.2062

(2R, 3S)-Methyl 4-(4-(tert-butyldimethylsiloxy)-3-(benzoyloxy)-2-hydroxybutoxy)benzoate (1e)

**Yield:** 81%, colorless liquid; [α]D^25^ -20.04 (c 1, CHCl₃); **IR** (CHCl₃, cm⁻¹): ν_max 771, 837, 1169, 1255, 1435, 1511, 1605, 1718, 2928, 3478; **¹H NMR** (200 MHz, CDCl₃) δ
0.09 (s, 6H), 0.91 (s, 9H), 2.94 (br s, 1H), 3.63- 3.68 (m, 1H), 3.81-3.96 (m, 5H), 4.07-4.17 (m, 3H), 4.53-4.74 (dd, $J = 11.6$ and $11.8$ Hz, 2H), 6.85-6.92 (m, 2H), 7.27 (m, 5H), 7.93-8.00 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 5.4, 18.2, 25.8, 51.7, 63.2, 69.0, 70.8, 72.7, 78.4, 114.1, 122.7, 127.8, 127.9, 128.3, 131.5, 137.9, 162.4, 166.6; Optical purity: 97% ee determined by HPLC analysis (OJ-H column, $n$-hexane/2-propanol (80:20), 0.5 mL/min, 254 nm) Retention time: $t_{\text{minor}} = 14.38$ and $t_{\text{major}} = 15.07$ min. HRMS (ESI): m/z Calcd for C$_{25}$H$_{36}$O$_6$NaSi [M + Na]$^+$, 483.2173; found, 483.2169.

(2R,3S)-1-(2,4,5-trichlorophenoxy)-4-(tert-butyldimethylsiloxy)-3-(benzyloxy)butan-2-ol (1)

Yield: 78%; gum; $[\alpha]_D^{25} +5.9$ (c 1.0, CHCl$_3$); IR (neat, cm$^{-1}$): $\nu_{\text{max}}$ 701, 763, 1050, 1261, 1454, 1492, 2104, 2935, 3034, 3416; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 0.09 (s, 6H), 0.92 (s, 9H), 2.88-2.95 (m, 1H), 3.64-3.71 (m, 1H) 3.84-3.91 (m, 2H), 4.06-4.13 (m, 3H), 4.52-4.75 (dd, $J = 11.7$, 2H), 6.93 (s, 1H), 7.28-7.30 (m, 5H), 7.43 (s, 1H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ -5.4, 18.3, 25.9, 63.4, 70.6, 70.9, 72.9, 78.2, 115.0, 122.1, 124.4, 127.9, 127.9, 128.1, 128.4, 130.8, 131.2, 137.9, 153.3; Optical purity: 97% ee determined by HPLC analysis (OJ-H column, $n$-hexane/2-propanol (90:10), 0.5 mL/min, 254 nm) Retention time: $t_{\text{minor}} = 14.38$ and $t_{\text{major}} = 15.07$ min.; HRMS (ESI): m/z Calcd for C$_{23}$H$_{36}$O$_6$NaSi [M + Na]$^+$, 527.0949; found, 527.0953.

(2R,3R)-1-[4-(Benzyloxy)-2-hydroxy-3-phenylpropoxy)phenyl]ethanone (2)

Yield: 89%; gum; $[\alpha]_D^{25} +21.56$ (c 1, CHCl$_3$); IR (neat, cm$^{-1}$): $\nu_{\text{max}}$ 701, 755, 1065, 1255, 1358, 1454, 1599, 1673, 3453; $^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 2.54 (s, 3H), 3.04 (br s, 1H), 3.74-3.80 (m, 1H), 3.97-4.16 (m, 2H), 4.30-4.56 (dd, $J = 11.2$ and 11.3 Hz, 2H), 4.61 (d, $J = 6.8$ Hz, 1H), 6.79-6.86 (m, 2H), 7.30-7.42 (m, 10H), 7.86 (m, 2H); $^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 26.2, 68.0, 70.8, 73.9, 81.4, 114.1, 127.4, 127.8, 127.9, 128.4, 128.5, 128.7, 130.4, 137.5, 137.8, 162.4, 196.2; Optical purity:
98% ee determined by HPLC analysis (Chiral OJ-H column, \textit{n}-hexane/ 2-propanol (70:30), 0.5 mL/min, 254 nm) Retention time: minor = 10.72 and $t_{major} = 11.28$ min.;

**HRMS** (ESI) m/z Calcd for C$_{24}$H$_{28}$O$_4$Na [M + Na]$^+$, 399.1567; found, 399.1567.
SECTION II:

Asymmetric Synthesis of D-erythro-Sphinganine via Co(III)-(salen) Catalyzed Two-Stereocentered HKR of Racemic Azido Epoxide

3.2.1 Introduction and pharmacology

Sphingolipids such as ceramides, cerebrosides and gangliosides are ubiquitous components of cell membranes. They play critical roles in many physiological processes including cell growth, differentiation, neuronal repair, cell recognition, adhesion, and signalling. Over the past decade, significant strides have been made in the elucidation of biological function of sphingolipids. One of the remarkable findings is the identification of sphingolipid metabolites as second messengers, which provides the basis for the emerging concept of sphingolipid metabolites as therapeutics with clinical potential. Common to this diverse group of natural products is a sphingoid base scaffold with a polar 2-amino alcohol head and a long aliphatic chain with or without a 4,5-trans double bond as in sphingosines (8 and 9) and sphinganine (7) or 2-amino-1,3,4 triol head group without unsaturation as in phytosphingosine (10).

![Structures of some sphingolipids](image)

Fig. 5: Structures of some sphingolipids

The hydrophilic moiety, located on the external surface of the membrane, determines the specificity of interactions, whereas the lipophilic portion, anchored on the outer-
leaflet, contributes primarily to the structural rigidity of the membrane. The most common naturally occurring sphingoid bases of animal and plant tissues are \textit{erythro}-sphinganine (7) and \textit{erythro}-sphingosine (8) (Fig. 5).

\textit{ribo}-Phytosphingosine is readily obtained on an industrial scale from yeast fermentation process. But the complicated isolation of other sphingolipids from natural sources, and the wide spectrum of the biological activity of these molecules justifies the efforts towards the synthesis of them as well as of their stereoisomers and various analogues.\textsuperscript{11-12} The most commonly employed strategies are those which make use of carbohydrates\textsuperscript{13} and serine\textsuperscript{14} as a source of chirality; many approaches are also based on asymmetric reactions, such as aldol condensation\textsuperscript{15} as well as Sharpless asymmetric dihydroxylation\textsuperscript{16} and asymmetric epoxidation (using Shi’s catalyst or Sharpless protocol\textsuperscript{17}). The design of an efficient and catalytic route to \textit{D-erythro}-sphinganine therefore continues to be important as it strongly inhibits protein kinase C.\textsuperscript{5,18} Thus the biological significance and the complicated isolation of sphingolipids from natural sources justifies the efforts towards their synthesis.

\textbf{3.2.2 Review of Literature}

Literature search revealed that there are more than hundred reports on the synthesis of the diastereomers of sphinganine. Many synthetic efforts have utilized starting materials derived from the chiral pool, in particular, carbohydrates, serine, and tartaric acid precursors.

\textbf{Ender’s approach (2004)}\textsuperscript{19}

The stereogenic centres are generated by $\alpha$-alkylation using the RAMP hydrazone methodology and diastereoselective reduction of the ketone 12 with L-selectride. In the first step hydrazone 11 was alkylated with pentadecyl bromide. Subsequently, hydrazone was cleaved with a saturated aqueous solution of oxalic acid to produce the
ketone 12 in excellent yield (96%) and enantiomeric excess (ee 96%). The ketone 12 was reduced with L-Selectride to give alcohol 13 in practically quantitative yield (98%) and very high diastereomeric excess (de 96%). Treatment of alcohol 13 with methanesulfonyl chloride yielded the corresponding mesylate 14 which was then converted into the azide 15 by nucleophilic substitution with sodium azide in DMF in the presence of 18-Crown-6. Reduction of the azide 15 with lithium aluminium hydride followed by hydrolytic cleavage of the acetonide group with trifluoroacetic acid in THF and water afforded the ammonium salt 16 with an overall yield of 47%, a diastereomeric excess of greater than 96% and an enantiomeric excess of greater than 96% (Scheme 3).

Scheme 3: i) t-BuLi, THF, -78 °C, then pentadecyl bromide, -100 °C; b) aq. oxalic acid; ii) L-Selectride, THF, -78 °C; iii) MsCl, CH₂Cl₂, Et₃N, 0 °C.; iv) NaN₃, 18-Crown-6, DMF, 100 °C; v) a) LiAlH₄, THF, 25 °C.; b) TFA, THF/H₂O, 25 °C.

Davies et al. (2008)²⁰

The synthesis of spinganine started with γ-silyloxy-α, β-unsaturated ester 18, which
was subjected to conjugate addition of lithium (S)-N-benzyl-N-(α-methylbenzyl) amide followed by enolate oxidation with (+)-CSO proceeded to generate the corresponding (2S,3S,αS)-α-hydroxy-β-amino-γ-silyloxy ester 19, which was isolated in good yield (91%), and >98% de. Reductive debenzylation of 19 and in situ boc protection afforded compound 20.

Scheme 4: (i) a) TBDMSCl, imidazole, DMAP, DCM, 25 °C, 12 h; b) O3, CH2Cl2, −78 °C, 30 min, then DMS, 25 °C, 12 h; c) (EtO)2P(=O)CH2CO2R, Pr3NEt, LiCl, MeCN, 48 h; (ii) lithium (S)-N-benzyl-N-(α-methylbenzyl)amide, THF, −78 °C, 2 h, then (+)-CSO, −78 °C to 25 °C, 12 h; (iii) H2 (5 atm), Pd(OH)2/C, Boc2O, EtOAc, 25 °C, 12 h; (iv) 2,2-dimethoxypropane, BF3·Et2O, acetone, 50 °C, 12 h. (v) a) LiAlH4, THF, 0 °C, 6 h; b) IBX, DMSO, rt, 12 h; (vi) C14H29PPh3+Br−, BuLi, THF–hexane (1 : 1), −78 °C to 25 °C, 12 h; (vii) H2 (1 atm), Pd/C, EtOAc, 25 °C, 6 h; (viii) a) HCl (3M, aq), MeOH, 50 °C, 3 h; b) Ac2O, DMAP, pyridine, 25 °C, 12 h.

Amino alcohol 20 was acetonide protected gave ester 21 followed by reduction with LiAlH4 and subsequent oxidation with IBX to give aldehyde 22. Compound 22 on Wittig olefination gave olefin 23, which was subjected to hydrogenation conditions.
and acetate protection to give \( N, O, O \)-triacetyl sphinganine 25 (Scheme 4).

**Lin’s approach (2008)**

This approach involves the \( \mathrm{SmI}_2 \)-mediated cross-coupling of \( N \)-tert-butanesulfinyl imines and aldehydes, which provides ready access to enantiopure \textit{anti}-1,2-amino alcohols. When palmitaldehyde 26 (4 equiv) was treated with imine 27 at -78 °C in THF, amino alcohol 28 was obtained as a single diastereomer in 64% yield. Removal of the benzyl and sulfinyl groups gave \textit{D-erythro}-sphinganine (7) in 90% yield with 97% ee. This approach represents one of the most convenient synthesis of 7 reported to date (Scheme 5).

![Scheme 5](image)

\textit{Scheme 5}: (i) \( \mathrm{SmI}_2, t\text{-BuOH}, 64\% \); (ii) a) Li/naphthalide, b) HCl, 90%

**Kumar’s approach (2013)**

The synthesis of sphinganine (7) started by treating commercially available 3-(benzyloxy) propanal 29 with 10 mol % of D-proline followed by the addition of dibenzyl azodicarboxylate (DBAD) in acetonitrile at 0 °C for 3 h. The reaction mixture having 30 in situ was diluted with THF/H₂O (3:1) and then reacted with indium powder and allyl bromide at room temperature for 12 h that produced homoallylic alcohol 31 in 72% yield. \textit{anti} Diasteromer was formed as a major product. Enantioselectivity was found to be 95% (chiral HPLC). The cross metathesis reaction between homoallylic alcohol 31 and tetradec-1-ene proceeded smoothly using 5 mol% of Grubbs’ second–generation catalyst in \( \mathrm{CH}_2\mathrm{Cl}_2 \) producing 32 in 85% yield. And finally the N-N bond in 32 was successfully cleaved and the double bond
was reduced simultaneously under hydrogenation conditions (Raney-Ni in MeOH and AcOH at 60 psi) to afford sphinganine (7) ([α]\text{D}^25 +9.8 (c 0.04, MeOH)] in 99% yield (Scheme 6).

\[ \text{BnOCHO} \xrightarrow{i} \text{BnOCbzNCHO} \xrightarrow{ii} \text{BnOCbzNHCbz} \]
\[ \xrightarrow{iii} \text{BnOCbzNHClz} \xrightarrow{iv} \text{Sphinganine (7)} \]

\text{Scheme 6: DBAD (1.2 equiv), D-proline (10 mol %), CH}_3\text{CN (0.1 M), } 0 \degree \text{C, 3 h;} \text{ In (2 equiv), 1-bromo-2-propene (2 equiv), CH}_3\text{CN-THF-H}_2\text{O (4:3:1) 25 \degree C, 12 h, 72%; tetradec-1-ene, Grubb's 2nd generation, 6 h, CH}_2\text{Cl}_2 \text{ 85%; H}_2 (60 \text{ psi), Raney Ni, MeOH, AcOH, 8 h, 99%}.\]

**Sutherland’s approach (2013)**

The synthesis began with the preparation of a suitable allylic alcohol substrate for the ether-directed Overman rearrangement. Initially, a chiral diol was prepared by the Sharpless asymmetric dihydroxylation of 1-heptadecene. Thus dihydroxylation of 33 gave diol 34 in >99% enantiomeric excess and in 87% yield. The primary and secondary hydroxyl groups of 34 were then selectively protected as TBDMS and MOM ethers, respectively, under standard conditions, giving 36 in quantitative yield. Removal of the TBDMS protecting group was followed by a one-pot Swern oxidation/Horner–Wadsworth–Emmons reaction of 37 with triethyl phosphonoacetate under Masamune-Roush conditions gave exclusively (E)-α,β-unsaturated ester 38.
DIBAL-H reduction of 38 gave allylic alcohol 39. Allylic alcohol 39 was transformed into the corresponding allylic trichloroacetimidate 40 using trichloroacetonitrile and DBU, and this was treated with bis(acetonitrile)palladium(II) chloride (10 mol%) to effect the key Overmann rearrangement. Analysis of the $^1$H NMR spectrum showed the presence of the erythro- 41 and threo-allylic trichloroacetamides in a 28:1 diastereomeric ratio, respectively, which was purified by column chromatography (major erythro diastereomer 41 in 78% yield from allylic alcohol 39).

Scheme 7: (i) AD-mix-$\beta$, t-BuOH/H$_2$O, 87%; (ii) TBDMSCl, imidazole, THF; (iii) MOMBr, EtNi-Pr$_2$, CH$_2$Cl$_2$, 100%; (iv) TBAF, THF, 91%; (v) DMSO, (COCl)$_2$ Et$_3$N, CH$_2$Cl$_2$, -78 °C; (vi) triethylphosphonoacetate, LiCl, DBU, MeCN, 100%; (vii) DIBAL-H, Et$_2$O, -78 °C, 86%; (viii) CCl$_3$CCN, DBU, CH$_2$Cl$_2$; (viiii) PdCl$_2$(MeCN)$_2$, p-benzoquinone, toluene, 45 °C, $dr =$ 28:1, 78%; (ix) O$_3$, MeOH, CH$_2$Cl$_2$, -78 °C, then NaBH$_4$, 78%; (x) 6M HCl, 60 °C, 100%.

To complete the synthesis of D-erythro-sphinganine, alkene 41 was subjected to ozonolysis followed by a reductive workup, gave alcohol 42 in 78% yield. Removal
of both protecting groups under acid-mediated conditions completed the 11-step synthesis of D-erythro-sphinganine 7 in 41% overall yield (Scheme 7).

**3.2.3 Present Work**

**3.2.3.1 Objective**

As can be seen from the above discussion, several methods for enantioselective synthesis of 7 or its isomers have been reported. Unfortunately, most of the reported methods for the synthesis of sphinganine (7), either employ chiral starting materials, expensive reagents or involve longer reaction sequences coupled with poor product selectivity. Despite recent improvements in the synthetic methodology for the control of the two stereo centers in the target molecule 7, most of them suffer either from poor diastereoselectivity, low overall yields, and/or a large number of steps involved. The development of an efficient and catalytic route to sphinganine therefore continues to attract the attention of chemists. As a part of our research program aimed at developing enantioselective syntheses of bioactive molecules, we became interested in developing a simple and feasible route to anti-amino alcohol 7. The section describes an enantioslective synthesis of D-erythro-sphinganine (7) via- Co(III)-salen (Fig. 6) catalyzed hydrolytic kinetic resolution (HKR) of azido epoxide as a key step for the introduction of chirality in the molecule (Scheme 9).

![Fig. 6: (R,R)-Co(III)-salen complex (43)](image-url)
3.2.3.2 Results and Discussion

Retrosynthetic analysis reveals that, for the synthesis of \textit{D-erythro}-sphinganine 1, alkene 52 was envisaged as the key intermediate, which could be easily prepared from (2S, 3S)-3-azido diol 48. We further visualized that diol 48 could be prepared from Co(III)salen-catalyzed HKR of racemic azido epoxide 46. The precursor epoxide 46 could be readily prepared from \textit{cis}-butene-1,4-diol 44 (Scheme 8).

\begin{center}
\includegraphics[width=\textwidth]{Scheme8.png}
\end{center}

\textbf{Scheme 8:} Retrosynthetic analysis of \textit{D-erythro}-sphinganine (7)

The synthesis of 7 commenced with bromoazidation of commercially available \textit{cis}-1,4-butenediol 44 in presence of NBS and NaN\textsubscript{3} followed by its base treatment (powdered NaOH, THF) gave racemic \textit{anti}-azido epoxy alcohol 45 in 84% yield and > 99% dr (Scheme 9). The epoxide formation was confirmed by \textit{^1}H and \textit{^{13}}C NMR spectroscopy. The \textit{^1}H NMR spectrum of 45 showed two typical multiplets at \(\delta\) 2.82-2.90 (m, 2H) and \(\delta\) 3.09-3.12 (m, 1H) for methylene (\textit{CH}_2\textit{O}) and methane (\textit{CH}_\textit{O}) protons respectively. Its \textit{^{13}}C NMR spectrum showed typical signals at \(\delta\) 45.0 and 50.3 due to primary and secondary carbons of epoxide ring respectively (Fig. 7).

The primary hydroxyl group in 45 was protected as its silyl ether 46 (TBDPSCI, imid., CH\textsubscript{2}Cl\textsubscript{2}). The formation of racemic silyl protected \textit{anti}-azido epoxide 46 was confirmed by \textit{^1}H NMR spectrum, which displayed signals at \(\delta\) 7.39-7.69 (m, 10H) for aromatic protons of diphenyl group and a typical singlet at \(\delta\) 1.08 (s, 9H) for the \textit{tert}-butyl group. Its \textit{^{13}}C-NMR showed typical signals at \(\delta\) 127.8-135.5 for diphenyl ring
carbons and δ 26.7 for tert-butyl group in the aliphatic region, which confirmed the formation of TBDPS protected azido epoxide 46 (Fig. 8).

The azido epoxide 46 was then subjected to HKR using \((R,R)-(salen)\) Co(III)(OCOCH\(_3\)) (43) as the catalyst that produced azido diol 48 in 46% yield and 97% ee along with the unreacted anti-azido epoxide 47 in 48% yield and 96% ee. Both 48 and 47 were however readily separated by column chromatography. The formation of anti-azidodiol 48 was confirmed by \(^1\)H and \(^{13}\)C NMR spectroscopy.
Fig. 7: $^1$H and $^{13}$C NMR spectra of Azido epoxide (45)
Fig. 8: $^1$H and $^{13}$C NMR spectra of ((S)-2-azido-2-((S)-oxiran-2-yl)ethoxy)(tert-butyl)diphenylsilane (46)
Fig. 9: $^1$H and $^{13}$C NMR spectra of (2S,3S)-3-Azido-(4-((tert-butyldiphenylsilyl)oxy)butan-1,2-diol (48)
The $^1$H NMR spectrum of *anti*-azidodiol 48 showed a typical signal at δ 3.89-3.97 (m, 2H) for methylene (-CH$_2$OH) protons and δ 2.0 and 2.64 for the two -OH protons of the diol. Its $^{13}$C NMR spectrum showed a characteristic carbon signal at δ 72.3 due to methine carbon (-CHOH) attached to hydroxyl group. Its HPLC chromatogram showed 97% ee (Fig. 9).

Fig. 10: $^1$H and $^{13}$C NMR spectra of (2S,3S)-3-azido-2-(tert-butyldimethylsiloxy-(4-((tert-butylidiphenylsilyl)oxy)butan-1-ol (50).
The diol 48 was protected as di-TBS ether 49, followed by the selective deprotection of the primary alcoholic silyl ether group in 49 with 10 mol% camphor sulfonic acid gave the primary alcohol 50 in 75% yield.

**Fig. 11:** $^1$H and $^{13}$C NMR spectra of (2S,3S)-3-azido-2-(tert-butyldimethylsiloxy)-(4-((tert-butyldiphenylsilyl)oxy)butan-1-al (51)
Fig. 12: $^1$H and $^{13}$C NMR and IR spectra of ((2S,3R)-2-azido-pent-4-en-1,3-yloxy)(tert-butyl)diphenyldimethylsilane (52)
The formation of 50 was confirmed by the display of characteristic signals at δ 0.00 integrating for 6 protons of dimethyl protons and two typical signals at δ 0.81 integrating for 9 protons of tert-butyl group in its $^1$H NMR spectrum, thus establishing the presence of only one TBS group. Its $^{13}$C NMR spectrum showed typical signal at δ 72.3 for methylenic carbon having free hydroxyl group (-CH$_2$OH) (Fig. 10).

![NMR spectra](image)

**Fig. 13:** $^1$H and $^{13}$C NMR of ((E,2S,3R)-2-azidooctadec-4-en-1,3-yloxy)(tert-butyl)diphenyldimethylsilane (54)

The alcohol 50 was then oxidized to the corresponding aldehyde 51 in 80% yield (IBX, EtOAc). The aldehyde 51 was confirmed from its characteristic singlet at δ 9.6
D-erythro-Sphinganine

(s, 1H) for aldehyde (-CHO) proton in its \(^1\)H NMR spectrum. A characteristic carbon signal at δ 201.1 due to -C=O group in its \(^{13}\)C NMR spectrum confirmed the formation of aldehyde 51 (Fig. 11).

The crude aldehyde 51 on Wittig reaction (PPh\(^3\)+CH\(_3\)I, \(n\)-BuLi, THF) gave the terminal alkene 52 in 65% yield over two steps. The formation of 52 was confirmed by the appearance of characteristic multiplets at δ 5.13-5.25 (m, 2H) for terminal alkenic protons (HC=CH\(_2\)) and δ 5.13-5.25 (m, 1H) for alkenic protons at secondary carbon in its \(^1\)H NMR spectrum. Its \(^{13}\)C NMR spectrum showed signals at δ 115.2 and 143.9 due to methylene (HC=CH\(_2\)) and methine (HC=CH\(_2\)) alkenic carbons respectively (Fig. 12).

The terminal alkene 52 was subjected to Ru-catalyzed cross metathesis with 1-pentadecene in the presence of Grubbs’ \(\text{II}^{\text{nd}}\) generation catalyst to obtain the crude long chain azido alkene 53. The synthesis of D-erythro-azidosphingosine 54 was achieved by the removal of silyl groups in crude long chain azido alkene 53 (TBAF in THF, 79% yield). The display of characteristic multiplets at δ 5.81 (m, 1H) and δ 5.74 (m, 1H) for alkenic protons confirmed the formation of long chain alkene. The disappearance of signals in the aromatic and aliphatic protons for the phenyl and tert-butyl groups in its \(^1\)H NMR spectrum confirmed the deprotection of both TBDPS and TBS groups. Its \(^{13}\)C NMR spectrum showed typical signals at δ 130.6 and 137 for the two alkenic carbons (-HC=CH-) and two characteristic signals at δ 79.2 and δ 68.8 corresponding to the (-CH\(_2\)OH) methylenic and methine (-CHOH) carbons respectively, having free hydroxyl group confirmed the formation of long chain alkene and deprotection of silyl ethers (Fig. 13).

Both the azido group and the alkene functionality in 54 were hydrogenated [H\(_2\) (1 atm), 10% Pd/C, MeOH/AcOH] to give D-erythro-sphinganine 7 ([\(\alpha\)]\(^{25}\)D +8.9 (c 0.04,
D-erythro-Sphinganine

MeOH)); lit.\textsuperscript{25} ([α]\textsubscript{D} +8.1 (c 1.0, MeOH)] in 6% overall yield and 97% ee (Scheme 9). The formation of 7 was confirmed by the disappearance of characteristic multiplets at δ 5.81 (m, 1H) and δ 5.74 (m, 1H) for alkenic protons (HC=CH) in its \textsuperscript{1}H NMR spectrum. Further the reduction of alkene in 54 was confirmed by the disappearance of signals for alkenic carbons (HC=CH) at δ 130.6 and 137 in its \textsuperscript{13}C NMR spectrum (Fig. 14).

\textbf{Fig. 14:} \textsuperscript{1}H and \textsuperscript{13}C NMR spectra of D-erythro-sphinganine (7)
3.2.4 Conclusion

In conclusion, we have achieved the synthesis of D-erythro-sphinganine (7) in 6% overall yield and 97% ee. The key intermediate, aldehyde 52 obtained via- Jacobsen Hydrolytic Kinetic Resolution of two- stereo centered azido epoxide 46 has been used as key step to introduce chirality.

3.2.5 Experimental

(S)-2-Azido-2-((S)-oxiran-2-yl)ethanol (45)

cis-Butenediol 44 (5 g, 56.81 mmol) was taken up in CH₂CN and H₂O mixture (30:10), and NaN₃ (7.38 g, 113.63 mmol) was added to it followed by the addition of N-bromosuccinimide (12.06 g, 68.18 mmol) slowly at 0 °C. After addition, the content was stirred for 4 h at 0 °C. To the reaction mixture water was added and the reaction mixture was extracted with EtOAc. The organic layer was separated and dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude product was used for next step without purification.

The crude product azido bromide (5 g, 25.90 mmol) was taken in dry THF and powdered NaOH (1.243 g, 31.08 mmol) was added slowly with stirring at 0 °C for 3 h. The reaction mixture was diluted with EtOAc (2 X 25 mL) followed by addition of water (30 mL). The organic layer separated and the aq. layer was extracted with EtOAc (2 X 20 mL). The combined organic extracts were washed with brine and dried over anhyd. Na₂SO₄ and concentrated under reduced pressure to give crude product. The crude product was purified by column chromatography over silica gel using CH₂Cl₂: Pet. ether: EtOAc (80:20:10) as an eluent to give pure azido epoxide 45.

Yield: 84%; gum; IR (CHCl₃, cm⁻¹): υ_max 702, 1427, 2105, 2837, 2961, 3472; ¹H NMR (200 MHz, CDCl₃): δ 2.18-2.21 (bs, 1H), 2.82-2.90 (m, 2H), 3.11-3.15 (m,
D-erythro-Sphinganine

1H), 3.47-3.49 (m, 1H), 3.71-3.84 (m, 2H); \(^{13}C\) NMR (50 MHz, CDCl\(_3\)): δ 44.24, 49.97, 61.85, 62.94; Analysis: C\(_4\)H\(_7\)N\(_3\)O\(_2\) requires: C, 37.21; H, 5.46; N, 32.54 found: C, 37.20; H, 5.45, N, 32.55 %.

\((S)-2\)-Azido-2-((S)-oxiran-2-yl)ethoxy\((tert\)-butyl)diphenylsilane (46)

To a stirred solution of epoxide 45 (12 g, 133.32 mmol) in dry CH\(_2\)Cl\(_2\) (200 ml), imidazole (13.59 g, 199.98 mmol) was added and the reaction mixture was cooled in ice-bath. \(tert\)-Butyldiphenyl silyl chloride (36.59 g, 133.32 mmol) was added slowly at 0 °C. After complete addition, the reaction mixture was stirred at room temperature for 6 h. After completion of reaction (monitored by TLC), it was diluted with CH\(_2\)Cl\(_2\) (40 ml) and washed with water (2×10 ml). Organic layer was dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. The residue was chromatographed over silica gel (60-120 mesh, EtOAc/hexane 19:1) yielding 46 as a colorless viscous oil.

Yield: 97%; viscous colorless liquid; IR (CHCl\(_3\), cm\(^{-1}\)): \(v_{\text{max}}\) 702, 1113, 1427, 2105, 2858, 2931; \(^1H\) NMR (200 MHz, CDCl\(_3\)): δ 1.08 (s, 9H), 2.72-2.81 (m 2H), 3.05-3.11 (m, 1H), 3.33-3.41 (q, J = 3.4 Hz, 1H), 3.81-3.84 (dd, J = 3.1 and 7.8 Hz, 2H), 7.35-7.45 (m, 6H); 7.65-7.69 (m, 4H); \(^{13}C\) NMR (50 MHz, CDCl\(_3\)): δ 19.1, 26.2, 45.0, 50.3, 63.5, 64.4, 127.8, 129.9, 132.6, 135.5; Analysis: C\(_{20}\)H\(_{25}\)N\(_3\)O\(_3\)Si requires: C, 65.36; H, 6.86; N, 11.43 found: C, 65.34; H, 6.83, N, 11.42 %.

\((2S,3S)-3\)-Azido-4-\((\text{tert}-\text{butyldiphenylsilyl})\)oxybutane-1,2-diol (48)

To a solution of \((R,R)\)-cobalt salen (43) (0.055 g, 0.09 mmol) in toluene (10 mL) was added glacial acetic acid. The solution was allowed to stir at 25 °C in open air for 30 min over which time color changed from orange-red to a dark brown and it was then concentrated in vacuo to get the Co-salen complex (Fig. 2) as a brown solid. To a solution of Co-salen complex (43) (0.055 g, 0.5 mol %) and azido epoxide 46 (6.70
D-erythro-Sphinganine

g, 18.26 mmol) in THF (2 mL) at 0 °C was added H₂O (0.12 g, 7.3 mmol) dropwise over 5 min. The reaction was allowed to warm to 25 °C and stirred for 14 h. After completion of reaction (monitored by TLC), solvent was removed in vacuo. The crude product was purified by column chromatography over silica gel using Pet.Ether: EtOAc (60:40) as eluent to give pure chiral anti-azidodiol 48 in 3.22 g.

Yield: 46%; [α]₂⁵ D : -59.30 (c 1, CHCl₃); Optical purity 97% ee from HPLC analysis:

Column: Chiracel OJ-H (4.6 X 250 nm), mobile phase: hexane/isopropyl alcohol (95/15), flow rate: 0.5 mL/min, retention time: 15.747 min (+)-isomer, 17.517 min (-)-isomer; IR (CHCl₃, cm⁻¹): v max 741, 1047, 1270, 1427, 2099, 2858, 2931, 3384; ¹H NMR (200 MHz, CDCl₃): δ 1.08 (s, 9H), 2.00 (s, 1H), 2.64 (bs, 1H), 3.50-3.55 (m, 1H), 3.71 (bs, 3H), 3.81-3.97 (m, 2H). ¹³C NMR (50 MHz, CDCl₃): δ 19.1, 25.7, 63.6, 64.8, 65.1, 72.3, 127.7, 129.6, 129.9, 134.8, 135.6. Analysis: C₂₀H₂₇N₃O₃Si requires: C, 62.31; H, 7.06; N, 10.90 found: C, 62.31; H, 7.07; N, 10.90 %.

(2S,3S)-3-Azido-2-(tert-butyldimethylsiloxy)-4-((tert-butyldiphenylsilyl)oxy)butan-1-ol (50)

A mixture of chiral diol 48 (3.98 g, 10.36 mmol), was taken in dry DMF (10 mL) to which imidazole (2.82 g, 41.45 mmol) was added followed by slow addition of TBS-Cl (6.24 g, 41.45 mmol) at 25 °C. The reaction mixture was stirred for 14 h at room temperature. Water was added to the reaction mixture and the product was extracted with EtOAc. The organic layer was concentrated under pressure. The crude compound was purified by column chromatography over silica gel using pet.ether: EtOAc (95:5) as eluent to give pure di-tert-butylsilyl ether 49 in 87% yield.

Pure di-TBS product 49 obtained (di-TBS) (4 g, 8.60 mmol) was taken up in 50 mL MeOH. To this, CSA (0.099 g, 0.43 mmol) was added at -25 °C. Reaction content was stirred for 30 min. After completion of reaction (monitored by TLC) to reaction saturated solution of ammonium chloride was added and the product was extracted
with CH₂Cl₂. The organic layer was separated and dried over anhyd. Na₂SO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography over silica gel using pet.ether : EtOAc (95:5) as eluent to give pure monoTBS 50 in 75% yield.

**Yield:** 75%; [α]²⁵_D: -22.20 (c 1, CHCl₃); **IR** (CHCl₃, cm⁻¹): υₘₐₓ 837, 1112, 1256, 2011, 2857, 2930, 3420; **¹H NMR** (200 MHz, CDCl₃): δ 0.07 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 3.52-3.82 (m, 6H), 4.49-4.63 (dd, J = 4.1 and 7.2 Hz, 2H), 7.26-7.33 (m, 5H); **¹³C NMR** (50 MHz, CDCl₃): δ -4.94, -4.57, 25.76, 62.69, 63.48, 69.43, 72.24, 73.44, 96.12, 127.67, 127.97, 128.43, 137.49; **Analysis:** C_{26}H_{41}N_{3}O_{3}Si_{2} requires: C, 62.48; H, 8.27; N, 8.41 found: C, 62.42; H, 8.19; N, 8.37%.

(2S,3S)-3-Azido-2-(tert-butyldimethylsiloxy-(4-(tert-butyldiphenylsilyl)oxy)butan-1-1-al (51)

To a stirred solution of oxalyl chloride i.e. (COCl)₂ (1.09 g, 4.27 mmol) in CH₂Cl₂ (30 mL) at -78 °C, was added a solution of DMSO (0.90 mL, 12.82 mmol). The reaction mixture was stirred for 20 min followed by the addition of alcohol 50 (1.5 gm, 4.27 mmol) in CH₂Cl₂ (20 mL). After stirring for 1 h the reaction was quenched by the addition of Et₃N (2.39 mL, 17.09 mmol). The reaction mixture was stirred for 30 min followed by the addition of water (10 mL). The organic phase was separated and aqueous phase extracted with CH₂Cl₂. Combined organic layer was washed with water, dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give crude aldehyde 51. The obtained product was sufficiently pure for characterization.

**Yield:** 80%; [α]²⁵_D = -8.52 (c 1, CHCl₃); **IR** (CHCl₃, cm⁻¹): υₘₐₓ 838, 1112, 1391, 1428, 1738, 2098, 2858, 2931; **¹H NMR** (200 MHz, CDCl₃): δ 0.42 (s, 6H), 0.93 (s, 9H), 3.54-3.71 (m, 3H), 4.15 (bs, 1H), 4.51 (d, J = 6.7 Hz, 2H), 7.26-7.30 (m, 5H), 9.55 (s, 1H); **¹³C NMR** (50 MHz, CDCl₃): δ -4.74, -5.09, 18.15, 25.70, 53.32, 62.82,
67.05, 73.46, 96.13, 127.65, 128.26, 137.37, 205.32; **Analysis**: C\textsubscript{26}H\textsubscript{39}N\textsubscript{3}O\textsubscript{3}Si\textsubscript{2}

requires: C, 62.73; H, 7.90; N, 8.44; found: C, 62.68; H, 7.89; N, 8.41 \%.

((2S,3R)-2-Azido-pent-4-en-1,3-yloxy)(tert-butyl)dimethyl-diphenylsilane (52)

To a stirred slurry of methylphosphonium bromide (1.1 g, 3.13 mmol) in THF (60 ml) at 0 °C was added n-BuLi (1.435 ml, 2.87 mmol, 2.07 M in Et\textsubscript{2}O) and the resultant solution was stirred at 0 °C for 10 min, followed by dropwise addition of the crude aldehyde 51 (1.3 g, 2.61 mmol) in THF (3 ml). After stirring at 0 °C for 1 h, reaction mixture was quenched by adding H\textsubscript{2}O (3 ml). After allowing the reaction mixture to warm to room temperature, it was diluted with water (10 mL) and extracted with Et\textsubscript{2}O (2 x 70 mL). The collected organic layer was washed with brine, dried over anhyd. Na\textsubscript{2}SO\textsubscript{4} and concentrated. The crude product was purified by column chromatography over silica gel (100-200 mesh) (hexane/EtOAc, 95:5) to give olefin 52 (0.84 g, 65%) as yellowish liquid.

**Yield**: 65%; yellowish liquid; **IR** (CHCl\textsubscript{3}, cm\textsuperscript{-1}): \(\nu_{\text{max}}\) 701, 837, 1113, 1255, 1471, 2100, 2858, 2957; **\textsuperscript{1}H-NMR** (200 MHz, CDCl\textsubscript{3}): \(\delta\) 0.01 (s, 6H), 0.83 (s, 9H), 1.08 (s, 9H), 3.59-3.76 (m, 3H), 4.22 (m, 1H); 5.13-5.30 (m, 2H); 5.68-5.85 (m, 1H); 7.35-7.43 (m, 6H); 7.62-7.69 (m, 4H); **\textsuperscript{13}C-NMR** (50 MHz, CDCl\textsubscript{3}): \(\delta\) -4.9, 19.2, 25.8, 26.8, 63.6, 68.2, 74.0, 117.1, 127.8, 129.8, 135.6, 137.1; **Analysis**: C\textsubscript{27}H\textsubscript{41}N\textsubscript{3}O\textsubscript{2}Si\textsubscript{2}

requires: C, 65.41; H, 8.34; N, 8.48 found: C, 65.38; H, 8.37; N, 8.38 \%.

(\textit{E})-(2S,3R)-2-Azido-octadec-4-ene-1,3-diol (54)

Grubbs’ second-generation catalyst (123.1 mg, 0.145 mmol) was added to a stirred solution of ((2S,3R)-2-azido-pent-4-en-1,3-yloxy)(tert-butyl)dimethyl-diphenylsilane 52 (0.717 g, 1.45 mmol) and pentadec-1-ene (0.912 g, 4.347 mmol) in CH\textsubscript{2}Cl\textsubscript{2} and stirring was continued for 12 h at 45 °C. When starting material was consumed completely, (checked by TLC), reaction mixture was concentrated and purified over
silica gel (100-200 mesh) chromatography (EtOAc/hexane 3:7) to yield alkene 53 (0.840 g) as a colorless oil, which was used directly for the next step.

The above crude silylprotected azidosphingosine 53 (0.800 g, 1.240 mmol) was dissolved in dry THF (30 ml), in which 1 molar solution of TBAF (0.806 g, 3.10 mmol) in THF was added at 25 °C and stirred for 8 h. After complete conversion of substrate into diol (monitored by TLC), reaction mixture was quenched with water (2 ml) at 0 °C and concentrated. The residue was dissolved in EtOAc and washed with brine, concentrated under reduced pressure and purified over silica gel (100-200 mesh) and pet ether/ethyl acetate (85:15) to give D-erythro-azidosphinganine 54 as a gummy solid (0.371 g, 79% over two steps).

**Yield:** 79%; gummy solid; [α]D25 -31.4 (c 0.8, CHCl3); lit.24 [α]D25 -32.9 (c 4, CHCl3); IR (CHCl3, cm⁻¹): υmax 3400, 2921, 2100, 1612; 1H NMR (200 MHz, CDCl3): δ 5.74-5.81 (dt, J = 14.5, 6.5 Hz, 1H), 5.50-5.65 (dd, J = 15.5, 6.2 Hz, 1H), 5.29 (d, J = 7.03 Hz, 1H), 4.31 (t, J = 4.7 Hz, 1H), 3.91-3.95 (dd, J = 11.2, 3.51 Hz, 1H), 3.68-3.72 (dd, J = 11.2, 3.51 Hz, 1H), 3.58 (s, 1H), 2.70 (s, 1H), 2.03-2.09 (q, J = 7.03 Hz, 2H) 1.35-1.39 (m, 2H), 1.26 (s, 22H), 0.89 (t, J = 6.53 Hz, 3H); 13C NMR (50 MHz, CDCl3): δ 14.1, 29.3, 29.5, 29.6, 31.9, 34.9, 65.5, 68.8, 79.2, 130.6, 137.4; Analysis: C18H35N3O2 requires: C, 66.42; H, 10.84; N, 12.91 found: C, 66.38; H, 10.80; N, 12.89 %.

**D-erythro-Sphinganine (7)**

To a stirred solution of D-erythro-azidosphingosine 54 (0.350 g, 1.07 mmol) in methanol (5 ml) was added 10% Pd/C (5 wt%). The reaction mixture was then stirred under H2 atmosphere (1 atm) at rt for 10 h. After completion of the reaction (monitored by TLC), the catalyst was filtered over Celite. The filtrate was concentrated under reduced pressure to give D-erythro-sphinganine 7 (0.316 g, 90%)
as a gum.

**Yield:** 90%: gum; \([\alpha]^{25}_D +8.9\) (c 0.8, MeOH); \([\alpha]^{25}_D +8.1\) (c 1.0, MeOH); **IR** (CHCl, cm\(^{-1}\)): \(v_{\text{max}}\) 3349, 2921, 1602, 1465, 1051; **H NMR** (200 MHz, CDCl): \(\delta\) 1.33 (t, \(J = 6.3\) Hz, 3H), 1.74 (s, 22H), 1.96 (s, 4H), 3.29 (bs, 3H), 4.04-4.17 (m, 2H); 4.37-4.42 (m, 2H); **C NMR** (50 MHz, CDCl): \(\delta\) 23.6, 32.6, 36.1, 37.8, 39.3, 39.6, 41.9, 74.2, 81.3, 103.7; **Analysis:** C\(_{18}\)H\(_{39}\)NO\(_2\) requires: C, 71.70; H, 13.04; N, 4.65 found: C, 71.67; H, 13.01; N, 4.63%.

### 3.2.6 References


6. (a) Reddy, R. S.; Chouthaiwale, P. V.; Suryavanshi, G.; Chavan, V. B.; Sudalai,
D-erythro-Sphinganine


