RSC Advances

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

'Chiron' approach to stereoselective synthesis of Sphinganine and unnatural Safingol, an antineoplastic and antipsoriatic agent

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Received (in XXX, XXX) Xth XXXXXXXXX 200X, Accepted Xth XXXXXXXXX 200X

DOI: 10.1039/b000000x

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Highly stereoselective total syntheses of sphingoid bases, natural bioactive ceramide sphinganine **1** (with an overall yield of 33%) and unnatural antineoplastic and antipsoriatic drug safingol **17** (with an overall yield of 38%) starting from chirons 3,4,6-tri-*O*-benzyl-D-galactal and 3,4,6-tri-*O*-benzyl-D-glucal respectively have been demonstrated. Mitsunobu reaction and late stage olefin cross metathesis are utilized as important steps in order to complete the total synthesis of these sphingoid molecules. .

Introduction

Sphingolipids possessing long chain 2-amino-1,3-diols motif are unique components of all eukaryotic cells. They are isolated from mammalian cells, plants, yeast, bacteria, fungi, viruses, marine organisms and in some prokaryotic organisms.[1] Due to intramolecular hydrogen bonding, these Sphingolipids bear a small positive charge at neutral pH that enables them to cross the membranes or move between membranes easily.[2] Sphingolipids and some of their metabolites play critical roles in various types of physiological processes that include cell regulation such as cell proliferation, differentiation, immune response, apoptosis, adhesion and signal transduction.[3] Recent studies have shown that deviation from sphingolipid metabolism causes several inherited and most common human diseases including diabetes, cancer, Alzheimer's disease, heart and infection by microorganisms.[3,4] Some of the representative sphingoid bases are shown in the figure 1.

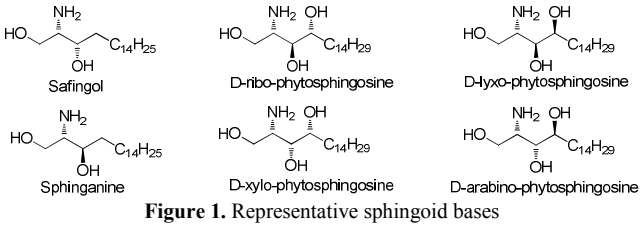


Figure 1. Representative sphingoid bases

Sphinganine and Safingol are sphingoid bases and are composed of three structural units: a long-chain aliphatic 2-amino-1,3-diol, a fatty acid and a polar head group. While the former is a naturally occurring base in D-*erythro*-(2*S*,3*R*)- configuration, the later one is among one of the three unnatural sphingoid bases in L-*thero*-(2*S*,3*S*)- configuration known. It has been observed that stereochemistry for both these compounds play a major role in their biological activities.[4]

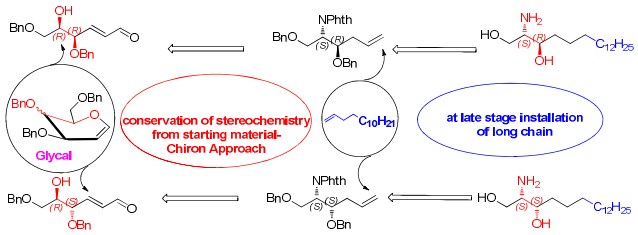
The variety of biological activities and unique stereostructures of both sphinganine and safingol substantiate a great deal of interest to access their economical synthetic route starting from commercially available precursors. Our group has been actively working on stereoselective synthesis of various types of biologically relevant molecules[5] including natural products from microorganisms,[6] plant[7] and marine origin[8,9] starting from commercially available chirons[10]. In continuation of our interest on chiron approach to synthesis of naturally occurring biomolecules, herein we wish to report on concise syntheses of title sphingoid bases starting from glycal derived enantiomerically pure α, β-unsaturated δ-hydroxy aldehydes commonly known as Perlin aldehydes.[11]

With our enduring interest in the syntheses of biologically active natural products or natural product like

molecules we are encouraged to undertake the synthesis of the bioactive natural products Sphinganine and Safingol from Perlin aldehydes as a chiral pool material.

Synthesis of Sphinganine and Safingol

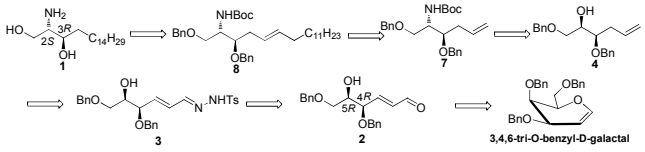
Synthesis of both the title molecules Sphinganine and Safingol must address two key concerns. First, the stereochemistry at the 2,3-amino alcohol unit and second the installation of long chain unit. In order to synthesize Sphinganine and Safingol, we started our synthetic route from 3,4,6-tri-*O*-benzyl-D-galactal and 3,4,6-tri-*O*-benzyl-D-glucal respectively in which the stereochemistry at 2,3-amino alcohol unit was inherited from the starting materials. The late stage olefin cross metathesis reaction was selected to install the long chain unit (Scheme 1).



Scheme 1. Synthetic plan towards Sphinganine and Safingol

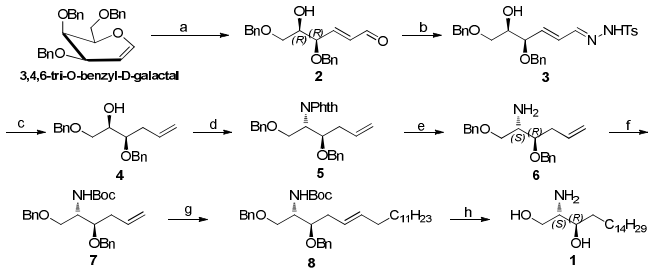
Synthesis of Sphinganine 1 (D-*erythro* (2*S*,3*R*) dihydrosphingosine)

Sphinganine **1** plays important roles in cell regulation and signal transduction. It is a biosynthetic intermediate of ceramides, sphingomyelin, cerebrosides and gangliosides.[12] It intensely inhibits protein kinase C6 and its ceramide derivatives are strong stimulators of the mammalian immune system.[2] It is an important part of symbioramide, a new type of bioactive ceramide, which is responsible for increasing sarcoplasmic reticulum Ca^{2+}- ATPase activity.[13] Because of its biological activities and the difficulties associated with the isolation in homogeneous form from natural sources, various synthetic methods have been reported to access it and its derivatives during last decades. Its earlier synthetic strategies were stereoselective by asymmetric routes or chiral pool material approaches.[2,14] But majority of them showed low levels of stereoselection resulting mixture of diastereoisomers and enantiomers that need to be separated. Recently, Wulff *et al.* demonstrated a general route for a catalytic asymmetric synthesis of its all four stereoisomers through multicomponent asymmetric aziridination whereas its total synthesis commencing from commercial N-*tert*-butyloxycarbonyl-L-serine methyl ester has been described by Siciliano and co-workers.[4,15] Thus, the literature reports revealed that highly stereoselective synthetic approach with less number of steps is still desirable today for those biologically relevant molecules whose isolation from the natural sources are either difficult or they are not found in the nature. Keeping this argument in mind, we designed the highly stereoselective synthesis of title natural product **1** based on its retrosynthetic analysis depicted in scheme 2. We envisaged that sphinganine **1** could be elaborated from the hydrogenolysis of **8**. The long chain sphingoid framework could be readily accessible from the olefin cross metathesis of Boc protected amine **7** with a suitable terminal olefin. The C2 amino functionality could be achieved by Mitsunobu reaction of the terminal olefin **4** with inversion of stereochemistry. The olefin could be simply obtained by $NaBH_4$ reduction of the hydrazone **3** which could in turn be prepared from Perlin aldehyde **2**[10] (Scheme 2).



Scheme 2. Retrosynthesis of Sphinganine **1**

Thus, the synthesis of **1** was started from easily avaiable 3,4,6-tri-*O*-benzyl-D-galactal derived Perlin aldehyde **2** which on treatment with 1.5 equiv. of tosylhydrazine at room temperature gave tosylhydrazone **3**. It was immediately allowed (without purification) to react with 10 equiv. of $NaBH_4$ in AcOH to obtain the terminal olefin **4** with 75% yield over two steps.[16] Its ^1H NMR spectra showing the disappearance of signal for aldehyde proton and appearance of signals for olefin protons at δ 5.1 and δ 5.9 confirmed the structure . It was then subjected to Mitsunobu reaction with pthalimide to furnish the pthalimido derivative **5** with 83% yield. The hydrolysis of the pthalimido functionality was done by treating **5** with methyl amine to produce the required free amine **6** whose immediate protection with $(Boc)_2O$ afforded the protected terminal olefin **7** with 95% yield over two steps.



Scheme 3. Synthesis of Sphinganine **1**.

Reagents and conditions: (a) ref 11; (b) $TsNHNH_2$, EtOH, 15min; (c) $NaBH_4$, AcOH, 75% (over two steps); (d) Pthalimide, DIAD (Diisopropyl azodicarboxylate), THF, -20 °C, 83%; (e) $MeNH_2$, DCM; (f) $(Boc)_2O$, Et_3N, DCM, 95% (over two steps); (g) 1-tetradecene, Grubbs' second generation catalyst, DCM, 45 °C, 70%; (h) Pd/C, H_2, TFA, 87%.

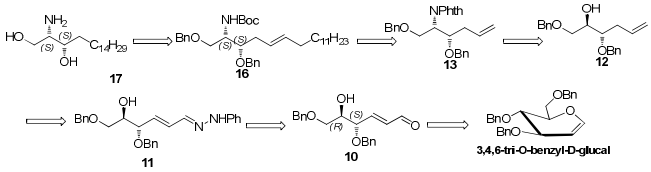
In order to complete the total synthesis of Sphinganine **1,** the long chain hydrocarbon was installed through the olefin cross metathesis reaction of **7** with 1-tetradecene in the presence of Grubbs' second generation catalyst in dichloromethane at 45 °C to obtain the unsaturated amine **8** in 70% yield. Finally, its global deprotection in the presence of Pd/C, H_2 and TFA provided the natural Sphinganine **1** with 33% overall yield (Scheme 3).

Synthesis of Safingol 17 (L-*thero*-(2*S*,3*S*)-dihydrosphingosine)

Safingol or L-*thero*-(2*S*,3*S*)-dihydrosphingosine **17** is an unnatural medicinally important sphingoid base. It is an antineoplastic and antipsoriatic drug[17] and plays significant role in cell regulation, signal transduction[12] and inhibits protein kinase C.[18] It synergistically increases the toxicity of established chemo- therapeutic agents in several cancer cells in vitro, as well as in preclinical animal studies and in a phase I clinical trial.[19]

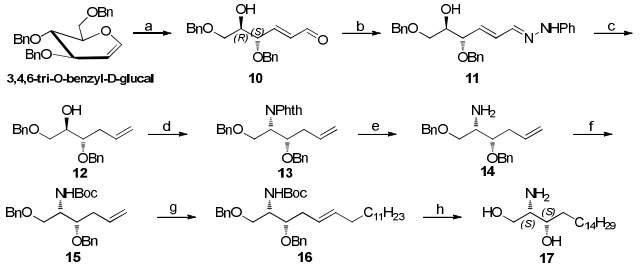
Owing to important biological activities of Safingol, a great deal of interest has been dedicated towards its total synthesis. The earlier reports on its syntheses include enantioselective stereoselective reduction of a chiral 2-acylaziridine intermediate,[20a] Pd-catalyzed isomerization of 5-vinyloxazolines by utilizing hydroboration/Suzuki coupling sequence to elongate the hydrophobic chain,[20b] asymmetric borane reduction of a ketone,[20c] nucleophilic addition to a chiral oxazolidinyl ester,[20d] Henry reaction,[20e] and multistep total synthesis starting from (Z)-but-2-ene-1,4-diol.[20f] The other literature methods reported during last one decade on its synthesis are based on kinetic resolution method,[21] palladium-catalyzed *trans*-oxazoline formation followed by cross metathesis,[22] a diastereoselective Grignard addition of a suitable alkylmagnesium bromide or lithium reagent to easily available (*R*) cyclohexylideneglyceraldehyde,[23] utilization of carbohydrate derived chiral pool material,[24] Sharpless kinetic resolution and tethered aminohydroxylation (TA),[25] chelation-controlled addition of an organocuprate species to protected α-amino aldehydes,[26] copper (II) catalyzed syn- and enantioselective Henry Reactions of aliphatic aldehydes,[27] palladium-catalyzed intramolecular aminohydroxylation of alkenes,[28] or from commercially available D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine[29] and *syn*-β-amino aldehyde prepared by (*R*)-proline catalyzes reaction between *N*-Boc-imine and aldehyde.[30]

Our retrosynthetic analysis envisioned (Scheme 4) for the synthesis of unnatural sphingoid base safingol **17** exhibiting L-*threo*-(2*S*,3*S*) configuration was similar to that of natural base sphinganine **1** occurring in D-*erythro* (2*S*,3*R*) configuration (Scheme 2)**.**



Scheme 4. Retrosynthesis of Safingol **17**.

Thus, the tosylhydrazone derivative **11**, the key intermediate, which was synthesized from 3,4,6-tri-O-benzyl-D-glucal derived Perlin aldehyde **10** by treating it with 1.5 equiv. of tosylhydrazine at room temperature on treatment with 10 equiv. of $NaBH_4$ in AcOH furnished the terminal olefin **12** with 70% yield over two steps.[16] The structure was established from its ^1H NMR spectra displaying signals in the olefinic region at δ 5.0 and 5.8 for the two protons and one proton respectively. Its Mitsunobu reaction with pthalimide provided the pthalimido derivative **13** with 83% yield. It was then subjected to undergo hydrolysis with methyl amine and the immediate protection of the resulting free amine with $(Boc)_2O$ resulted the protected terminal olefin **15** with 96% yield over two steps.



Scheme 5. Synthesis of Safingol **17**.

Reagents and conditions: (a) ref 11; (b) $TsNHNH_2$, EtOH, 15min; (c) $NaBH_4$, AcOH, 70% (over two steps); (d) pthalimide, DIAD (Diisopropyl azodicarboxylate), THF, -20 °C, 83%; (e) $MeNH_2$, (f) $(Boc)_2O$, Et_3N, DCM, 96% (over two steps); (g) 1-tetradecene, Grubbs' second generation catalyst, DCM, 45 °C, 76%; (h) Pd/C, H_2, TFA, 92%.

After constructing the polar head group (2*S*,3*S* 2-amino 1,3 diol) of title molecule, the long chain hydrocarbon was installed by

olefin cross metathesis between 1-tetradecene and **15** in the presence of Grubbs' second generation catalyst in DCM at 45 °C to obtain the olefinic compound **16** in 76% yield. Its benzyl deprotection and reduction of olefin functionality were achieved in one pot in the presence of Pd/C, H_2 and TFA resulting in the formation of unnatural sphingoid, Safingol **17** with an overall yield of 38% (Scheme 5). The spectral data of both the title natural and unnatural products are in good agreement with those reported in the literature. {Sphinganine **1** $[\alpha]_D^{27}$ +7.8 (c 0.16, EtOH) Lit[2,15]: $[\alpha]_D$ 8.1, c 1.0, CH_3OH), $[\alpha]_D$ 7.9, c 1.0, CH_3OH); Safingol **17** $[\alpha]_D^{27}$ -7.5 (c 0.09, EtOH) [Lit[27]: $[\alpha]_D$ [20] -4.0 (*c* 0.5 in $CHCl_3$), $[\alpha]_D$ -11.2 (*c* 0.10, $CHCl_3$:CH_3OH, 10:1, v/v)]}.

Conclusion

In summary, the highly stereoselective total syntheses of natural Sphinganine **1** and antineoplastic and antipsoriatic drug Safingol **17**[17] were accomplished starting from chirons 3,4,6-tri-*O*-benzyl-D-galactal and 3,4,6-tri-*O*-benzyl-D-glucal respectively. The stereochemistries at C2 and C3 in Sphinganine (2*S*,3*R*) and Safingol (2*S*,3*S*) were directed by the Perlin aldehydes **2** and **10** respectively. The 2S stereochemistry in both the target molecules was achieved by Mitsunobu reaction and their stereochemistry at C3 was conserved from the C4 of their respective unsaturated aldehydes **2** and **10**. Late stage olefin cross metathesis reaction was employed to install the long chain hydrocarbon, thus completing the synthesis of title molecules. Our synthetic strategies for both the molecules were similar and all the reagents including the starting materials are commercially and easily available. Thus, it is worth mentioning that both the schemes 3 and 5 are highly cost effective for their commercialization.

Experimental

Organic solvents were dried by standard methods. Analytical TLC was performed using 2.5 × 5 cm plates coated with a 0.25 mm thickness of silica gel (60F-254), visualization was done with CeSO4 and subsequent charring over a hot plate. Silica gel (60–120 mesh) and silica gel (230–400 mesh) were used in column chromatography. All the products were characterized by using ^1H, ^{13}C, IR and ESI-HRMS. NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer at 300 MHz (^1H) and 75 MHz (^{13}C), 400 MHz spectrometer at 400 MHz (^1H) and 100 MHz (^{13}C). Experiments were performed in $CDCl_3$ and CD_3OD at 25 °C. Chemical shifts are given on the δ scale and are referenced to TMS at 0.00 ppm for a proton and 0.00 ppm for carbon. For ^{13}C NMR reference $CDCl_3$ appeared at 77.40 ppm and CD_3OD appeared at 48.70 ppm. IR spectra were recorded on Perkin-Elmer 881 and FTIR-8210 PC Shimadzu Spectrophotometers. Optical rotations were determined on an Autopol III Polarimeter and a DigiPol 781M6U NOVA Polarimeter using a 1 dm cell at 17 °C–32 °C in chloroform and methanol and ethanol as the solvents; concentrations mentioned are in g per 100 mL. Mass spectra were recorded on a JEOL JMS-600H high resolution spectrometer using EI mode at 70 eV. ESI-HRMS were recorded on a JEOL-AccuTOF JMS-T100LC spectrometer. ESI-HRMS were recorded on a JEOL-AccuTOF JMS-T100LC spectrometer.

Synthesis of compound (2R,3R)-1,3-bis(benzyloxy)hex-5-en-2-ol (compound 4)

The Perlin aldehyde **2** (1g, 3.07 mmol) and *p*-toluenesulfonylhydrazine (856 mg, 4.06mmol) in absolute ethanol (2 ml) were stirred at room temperature until a clear solution resulted (15 min). The solvent was evaporated after completion of the reaction. To the crude tosylhydrazone **3** (1.5 g, 3.6 mmol) of glacial acetic acid was added $NaBH_4$ (1g, 30 mmol) at 0 °C with a precaution that foaming was avoided. The solution was stirred at room temperature for 2h. The solution was then poured into crushed ice, treated with aqueous NaOH to make it basic, and extracted with three portions of diethylether (10mL each). The ether solution was dried and concentrated on a rotary evaporator and purified by column chromatography to obtain pure terminal olefin **4** (720 mg, 2.3 mmol) in 75% yield.

Eluent for column chromatography: EtOAc/Hexane (1/9, v/v); $[\alpha]_D^{27}$ -24.3 (c 0.23, $CHCl_3$); R_f= 0.5 (1/4, EtOAc/Hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 2.41-2.49 (m, 3H), 3.56-3.57 (m, 2H), 3.63-3.65 (m, 1H), 3.84-3.85(dd, J_1= 5.44, J_2= 9.93 Hz, 2H), 4.50-4.56 (m, 3H), 4.68-4.71 (m, 1H), 5.09-5.17 (m, 2H), 5.85-5.89 (m, 1H), 7.28-7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.0, 71.1, 71.6, 72.6, 73.5, 78.6, 117.7, 127.8, 127.9, 128.0, 128.1, 128.5, 128.7, 134.5, 138.1, 138.3; IR (neat, cm^{-1}): 668, 698, 770, 1068, 1217, 1403, 1639, 2926, 3017, 3400; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}O_3^+$ 313.1798, measured 313.1798.

2-((2S,3R)-1,3-bis(benzyloxy)hex-5-en-2-yl)isoindoline-1,3-dione (compound 5)

A solution of phthalimide (458 mg, 3.12 mmol), triphenyl phosphine (817 mg, 3.12 mmol) and the alcohol **4** (650 mg, 2.08 mmol), in dry THF (20 mL) was cooled to –20 ˚C under argon atmosphere. DIAD (0.6 mL, 3.12 mmol) was added drop wise to the above solution. The resulting mixture was stirred at the same temperature for 2 h and afterward at room temperature. After overnight stirring, the reaction mixture was evaporated under reduced pressure to give a residue which on column chromatographic purification provided the compound **5** (760 mg, 1.72 mmol) in 83 % yield.

Eluent for column chromatography: EtOAc/Hexane (1/9, v/v); $[\alpha]_D^{27}$ -48.4 (c 0.31, $CHCl_3$); R_f= 0.6 (1/4, EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.15-2.19 (m, 1H), 2.33-2.38 (m, 1H), 3.83-3.86 (dd, J_1= 4.32, J_2= 10.22 Hz, 1H,), 4.02-4.05 (t, J = 9.96 Hz, 1H), 4.14-4.17 (m, 1H), 4.31-4.34 (m, 1H), 4.41-4.45 (m, 2H), 4.56-4.57 (m, 1H), 4.58-4.59 (m, 1H), 4.88-4.92 (m, 2H), 5.73-5.78 (m, 1H), 7.09-7.17 (m, 5H), 7.19-7.26 (m, 5H), 7.73-7.74 (m, 2H), 7.74-7.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 35.8, 53.5, 67.3, 72.2, 72.7, 76.2, 117.9, 123.4, 123.5, 127.6, 127.7, 127.9, 128.0, 128.4, 128.5, 128.7, 128.8, 132.0, 133.6, 134.0, 134.1, 138.1, 138.2, 168.7; IR (neat, cm^{-1}): 668, 698, 721, 757, 768, 1068, 1216, 1386, 1639, 1711, 1774, 2926, 3019, 3399; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_4^+$ 442.2013, measured 442.2010.

tert-butyl ((2S,3R)-1,3-bis(benzyloxy)hex-5-en-2-yl)carbamate (compound 7)

The pthalimide **5** (700 mg, 1.58 mmol) was dissolved in aqueous solution of $MeNH_2$ (10 mL, 40 %), and the resulting mixture was stirred in an open flask for 3 h at 60 °C. The reaction mixture was then concentrated under reduced pressure, dissolved in water (15 mL) and extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by passing it through a filter column. To a stirred solution of amine **6** (460 mg, 1.47 mmol) in DCM (20 mL) at 0 °C was added Et_3N (0.3 mL, 2.2 mmol) and the stirring was continued for 10 min at the same temperature. After 10 min, Boc_2O (0.5 mL, 4.7 2.2 mmol) was added dropwise. The resulting reaction mixture was then allowed to warm to room temperature and stirred for an additional 4 h. Water was then added to the reaction mixture and the reaction mixture was extracted with DCM (3 × 10 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography to afford olefin **7** (620 mg, 1.50 mmol) in 95 % yield over two steps.

Eluent for column chromatography: EtOAc/Hexane (3/97, v/v); $[\alpha]_D^{27}$ -13.0 (c 0.22, $CHCl_3$); R_f= 0.6 (1/19, EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 9H), 2.37-2.45 (m, 2H), 3.57-3.60 (dd, J_1= 3.63, J_2= 9.31 Hz, 1H), 3.66-3.68 (m, 1H), 3.76-3.80 (m, 1H), 3.94 (brs, 1H), 4.47-4.65 (m, 4H), 4.91-4.93 (m, 1H), 5.10-5.17 (m, 2H), 5.88-5.99 (m, 1H), 7.28-7.30 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5, 35.7.0, 52.5, 69.1, 72.4, 73.3, 78.5, 79.4, 117.6, 127.8, 128.0, 128.48, 128.5, 134.8, 138.3, 138.5, 155.6; IR (neat, cm^{-1}): 668, 758, 920, 1028, 1066, 1162, 1215, 1366, 1391, 1499, 1708, 2927, 3018, 3436; ESI-HRMS: *m/z* $[M+Na]^+$ calcd for $C_{25}H_{33}NaNO_4^+$ 434.2302, measured 434.2300.

***tert*-butyl ((2S,3R,E)-1,3-bis(benzyloxy)octadec-5-en-2-yl)carbamate (compound 8)**

To a 50 ml two necked oven dried round bottomed flask fitted with reflux condenser and septum was added Grubbs' second generation catalyst (10 mg, 0.012 mmol) under argon atmosphere. The olefin **7** (100 mg, 0.24mmol) in dry DCM and 1-tetradecene (0.25mL, 0.96mmol) were added simultaneously through a syringe to the above flask. The reaction mixture was then degassed. The septum was replaced with a glass stopper while the stirring was continued. The solution was refluxed for 6 h. The temperature of the reaction mixture was cooled slowly to room temperature. The organic solvent was evaporated under reduced pressure to give a brown residue, which was directly purified by column chromatography (230-400 mesh) to furnish pure compound **8** as a colourless oil (97 mg, 0.16 mmol, 70%).

Eluent for column chromatography: EtOAc/Hexane (3/97, v/v); $[\alpha]_D^{27}$ -7.2 (c 0.16, $CHCl_3$); R_f= 0.7 (1/20, EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89-0.92 (m, 3H), 1.27 (s, 21H), 1.99 (s, 9H), 2.00-2.02 (m, 2H), 2.31-2.40 (m, 2H), 3.56-3.64 (m, 2H), 3.73-3.76 (m, 1H), 3.93 (brs, 1H), 4.46-4.56 (m, 3H), 4.62-4.66 (m, 1H), 4.89-4.91 (m, 1H), 5.49-5.53 (m, 2H), 7.31-7.36 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.8, 28.6, 29.4, 29.5, 29.6, 29.7, 29.8, 29.84, 32.1, 32.9, 34.6, 52.6, 69.2, 72.5, 73.2, 79.0, 125.8, 127.7, 127.8, 128.0, 128.5, 133.8, 138.4, 138.7, 155.6; IR (neat, cm^{-1}): 763, 1065, 1159, 1217, 1394, 1499, 1641, 2925, 3403; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{37}H_{58}NO_4^+$ 580.4360, measured 580.4357.

(2S,3R)-2-aminooctadecane-1,3-diol (Sphinganine 1)

To a solution of **8** (50 mg, 0.08 mmol) in MeOH (3 mL), trifluoroacetic acid (0.2 mL, 2.51 mmol) was added and degassed. Next, $Pd(OH)_2/C$ (10mg) was added to the reaction mixture and stirred under hydrogen atmosphere (balloon) for 12 h. After completion of the reaction (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with 1:1 MeOH/$CHCl_3$ (10 mL). The residue obtained after concentration of the solvent was purified by column chromatography using MeOH/$CHCl_3$ (1:4) as eluent to furnish the Sphinganine **1** (21 mg, 0.07 mmol) in 81% yield.

$[\alpha]_D^{27}$ +7.9 (c 0.16, EtOH); R_f= 0.3 (1/4/1, MeOH/$CHCl_3$/NH_4OH); ^{1}H NMR (400 MHz, CD_3OD): δ 0.93-0.94 (m, 3H), 1.31-1.33 (m, 24H), 1.51 (brs, 4H), 3.33 (brs, 1H), 3.69-3.77 (m, 1H), 3.81-3.88 (m, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 13.4, 22.7, 26.0, 29.5, 29.6, 29.8, 32.1, 33.2, 57.5, 57.9, 69.3; IR (KBr, cm^{-1}): 668, 770, 1067, 1216, 1403, 1638, 2849, 2918, 3019, 3391; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{18}H_{40}NO_2^+$ 302.3054, measured 302.3054.

Synthesis of compound (2R,3S)-1,3-bis(benzyloxy)hex-5-en-2-ol (compound 12)

The Perlin aldehyde **10** (1g, 3.07 mmol) and *p*-toluenesulfonylhydrazine (856 mg, 4.06mmol) in absolute ethanol (2 ml) were stirred in a RB flask at room temperature until a clear solution resulted (15 min). After the completion of the reaction, the solvent was evaporated. To the crude tosylhydrazone **11** (1.5 g, 3.6 mmol) in 15 mL of glacial acetic acid was added $NaBH_4$ (1g, 30 mmol) at 0°C slowly to avoid foaming. The solution was stirred at room temperature for 2h. Afterward, it was poured into crushed ice, made basic with aqueous NaOH, and extracted with three portions of diethylether (10mL each). The ether solution was dried and concentrated on a rotary evaporator and purified by column chromatography to furnish pure terminal olefin **12** (670 mg, 2.14mmol) in 70% yield.

Eluent for column chromatography: EtOAc/Hexane (1/9, v/v); $[\alpha]_D^{27}$ +28.3 (c 0.36, $CHCl_3$); R_f= 0.5 (1/4, EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.32-2.36 (m, 2H), 2.40-2.41 (d, J= 4.95Hz, 1H), 3.45-3.51 (m, 2H), 3.54-3.58 (m, 1H), 3.75-3.79 (m, 1H), 4.40-4.45 (m, 3H), 4.51-4.54 (m, 1H), 4.98-5.03 (m, 1H), 5.07-5.08 (m, 1H), 5.78-5.85 (m, 1H), 7.18-7.27 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 34.8, 71.1, 71.6, 72.3, 73.5, 79.2, 117.5, 127.8, 128.0, 128.5, 128.6, 134.7, 138.0, 138.4; IR (neat, cm^{-1}): 667, 698, 756, 917, 1027, 1071, 1216, 1407, 1454, 1496, 1640, 2923, 3013, 3412; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{20}H_{25}O_3^+$ 313.1798, measured 313.1792.

Synthesis of compound 2-((2S,3S)-1,3-bis(benzyloxy)hex-5-en-2-yl)isoindoline-1,3-dione (compound 13)

A solution of phthalimide (458 mg, 3.12 mmol), triphenyl phosphine (817 mg, 3.12 mmol) and the alcohol **12** (650 mg, 2.08 mmol), in dry THF (20 mL) was cooled to −20 ˚C under argon atmosphere. DIAD (Diisopropyl azodicarboxylate) (0.6 mL, 3.12 mmol) was added drop wise to the above solution. The reaction mixture was stirred at the same temperature for 2 h and then at room temperature. After overnight stirring, the reaction mixture was evaporated under reduced pressure to give a residue which on column chromatographic purification provided the compound **13** (760 mg, 1.72 mmol) in 83% yield.

Eluent for column chromatography: EtOAc/Hexane (1/9, v/v); $[\alpha]_D^{27}$ +29.5 (c 0.16, $CHCl_3$); R_f= 0.6 (1/4, EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.16-2.22 (m, 1H), 2.44-2.49 (m, 1H), 3.66-3.70 (dd, J_1= 4.9, J_2 = 10.2 Hz, 1H), 3.96-4.01 (m, 1H), 4.02-4.06 (m, 1H), 4.24-4.27 (m, 1H), 4.34-4.37 (m, 1H), 4.41-4.44 (m, 1H), 4.49-4.57 (m, 2H), 5.02-5.03 (m, 1H), 5.06 (s, 1H), 5.83-5.87 (m, 1H), 6.98 (s, 5H), 7.13-7.17 (m, 5H), 7.58-7.61 (m, 2H), 7.67-7.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.0, 54.1, 66.5, 72.1, 72.8, 76.0, 118.3, 123.2, 123.4, 127.4, 127.7, 127.8, 128.2, 128.4, 128.7, 132.1, 133.5, 133.8, 137.9, 138.2, 168.7; IR (neat, cm^{-1}): 531, 668, 758, 920, 1027, 1073, 1217, 1389, 1639, 1710, 1772, 2926, 3022, 3409; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{28}H_{28}NO_4^+$ 442.2013, measured 442.2007.

Synthesis of compound tert-butyl ((2S,3S)-1,3-bis(benzyloxy)hex-5-en-2-yl)carbamate (compound 15)

The pthalimido derivative **13** (700 mg, 1.58 mmol) was dissolved in aqueous solution of $MeNH_2$ (10 mL, 40 %), and the resulting mixture was stirred in an open flask for 3 h at 60 °C. The reaction mixture was then concentrated under reduced pressure, dissolved in water (15 mL) and extracted with ethyl acetate (4 × 10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude was purified by passing it through a filter column. To a stirred solution of amine **14** (460 mg, 1.47 mmol) in DCM (20 mL) at 0 ˚C was added Et_3N (0.3 mL, 2.2 mmol) and the stirring was continued for 10 min at the same temperature. After 10 min, Boc_2O (0.5 mL, 4.7 2.2 mmol) was added dropwise. The resulting reaction mixture was then allowed to warm to room temperature and stirred for an additional 4 h. Water was then added to the reaction mixture and the reaction mixture was extracted with DCM (3×10 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and evaporated under reduced pressure. The crude residue was purified by silica gel column chromatography to afford olefin **15** (620 mg, 1.5 mmol) in 95% yield over two steps.

Eluent for column chromatography: EtOAc/Hexane (3/97, v/v); $[\alpha]_D^{27}$ +33.1 (c 0.24, $CHCl_3$); R_f= 0.6 (1/19, EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H), 2.22-2.24 (m, 1H), 2.32-2.39 (m, 1H), 3.37-3.42 (m, 2H), 3.68-3.71 (t, J_1= 5.78, J_2= 12.04 Hz, 1H), 3.85-3.91 (m, 1H), 4.32-4.45 (m, 3H), 4.52-4.55 (m, 1H), 4.77-4.79 (d, J=9.54 Hz, 1H), 4.99-5.07 (m, 2H), 5.71-5.81 (m, 1H), 7.17-7.27 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.5, 36.0, 51.8, 69.5, 72.8, 73.1, 77.0, 79.4, 117.9, 127.7, 127.8, 127.9, 128.1, 128.5, 134.5, 138.3, 138.4, 155.8; IR (neat, cm^{-1}): 766, 1062, 1161, 1218, 1406, 1499, 1639, 1704, 3432; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{25}H_{34}NO_4^+$ 412.2482, measured 412.2472.

Synthesis of compound tert-butyl ((2S,3S,E)-1,3-bis(benzyloxy)octadec-5-en-2-yl)carbamate (compound 16)

To a 50 ml two necked oven dried round bottomed flask fitted with reflux condenser and septum was added Grubbs' second generation catalyst (10 mg, 0.012 mmol) under argon atmosphere. The olefin **15** (100 mg, 0.24mmol) in dry DCM and 1- tetradecene (0.25mL, 0.96mmol) were added simultaneously through a syringe to the above flask. The reaction mixture was then degassed. The septum was replaced with a glass stopper while the stirring was continued. The solution was refluxed for 6 h. The temperature of the reaction mixture was cooled slowly to room temperature. The organic solvent was evaporated under reduced pressure to give a brown residue, which was directly purified by column chromatography (230-400 mesh) to furnish pure compound **16** as a colourless oil (105 mg, 0.18 mmol, 76%).

Eluent for column chromatography: EtOAc/Hexane (3/97, v/v); $[\alpha]_D^{27}$ +5.1 (c 0.36, $CHCl_3$); R_f= 0.7 (1/20, EtOAc/Hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79-0.82 (m, 3H), 1.18-1.23 (m, 19H), 1.35 (s, 9H), 1.88-1.99 (m, 2H), 2.14-2.30 (m, 2H), 3.37-3.47 (m, 2H), 3.62-3.87 (m, 2H), 4.19-4.56 (m, 4H), 4.76-4.78 (m, 1H), 5.31-5.46 (m, 2H), 7.18-7.25 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.8, 28.5, 29.4, 29.5, 29.6, 29.7, 29.8, 32.1, 32.5, 32.9, 34.8, 51.9, 69.6, 70.3, 72.9, 73.1, 78.1, 79.3, 125.5, 127.6, 127.8, 127.9, 128.1, 128.5, 133.0, 134.2, 136.2, 138.4, 138.6, 155.8; IR (neat, cm^{-1}): 668, 698, 757, 1027, 1068, 1158, 1216, 1405, 1454, 1497, 1639, 1706, 2854, 2926, 3017, 3434; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{37}H_{58}NO_4^+$ 580.4360, measured 580.4357.

(2S,3S)-2-aminooctadecane-1,3-diol (Safingol 17)

To a solution of **16** (50 mg, 0.08 mmol) in MeOH (3 mL), trifluoroacetic acid (0.2 mL, 2.51 mmol) was added and degassed. Next, $Pd(OH)_2/C$ (10mg) was added to the reaction mixture and stirred under hydrogen atmosphere (balloon) for 12 h. After completion of the reaction (TLC), it was filtered through a short pad of Celite and the Celite pad was washed with 1:1 $MeOH/CHCl_3$ (10 mL). The residue obtained after concentration of the solvent was purified by column chromatography using $MeOH/CHCl_3$ (1:4) as eluent to furnish the TFA salt of Safingol **17** salt (22 mg, 0.07 mmol) in 92 % yield as a white solid. mp 106–111 °C;

$[\alpha]_D^{27}$ -7.6 (c 0.09, EtOH); R_f= 0.3 (1/4/1, MeOH/$CHCl_3$/NH_4OH); ^1H NMR (400 MHz, CD_3OD): δ 0.88-0.91 (m, 3H), 1.29 (s, 25H), 1.54 (brs, 3H), 3.03- 3.08 (m, 1H), 3.63-3.70 (m, 2H), 3.70-3.80 (dd, J_1= 4.04, J_2= 11.7 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 14.4, 23.7, 26.3, 30.4, 30.6, 30.8, 33.0, 34.9, 59.1, 60.5, 69.1; IR (KBr, cm^{-1}): 669, 770, 1067, 1216, 1403, 1637, 2852, 2922, 3019, 3399; ESI-HRMS: *m/z* $[M+H]^+$ calcd for $C_{18}H_{40}NO_2^+$ 302.3054, measured 302.3051.

Acknowledgements

We are thankful to Mr. A. K. Pandey for technical assistance and SAIF, CDRI for providing spectral data. Pintu Das and Somireddy Kundooru thank CSIR for awarding Senior Research Fellowship and both contributed to the present work equally. CDRI manuscript no. 315/2015/AKS.

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‘Chiron’ approach to stereoselective synthesis of Sphinganine and unnatural Safingol, an antineoplastic and antipsoriatic agent

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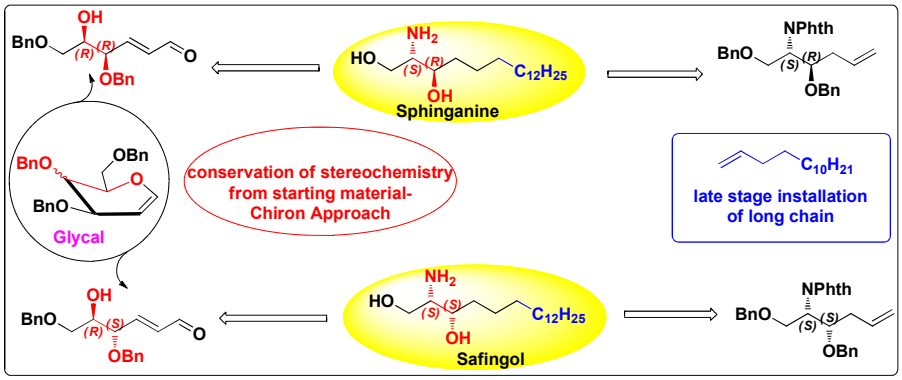

Highly stereoselective total syntheses of sphingoid bases, natural bioactive ceramide sphinganine **1** (with an overall yield of 33%) and unnatural antineoplastic and antipsoriatic drug safingol **17** (with an overall yield of 38.2%) starting from chirons 3,4,6-tri-O-benzyl-D-galactal and 3,4,6-tri-O-benzyl-D-glucal respectively have been demonstrated. Mitsunobu reaction and late stage olefin cross metathesis are utilized as important steps in order to complete the total synthesis of these sphingoid molecules.