Stereoselective Transformation of Phytosphingosine to Safingol

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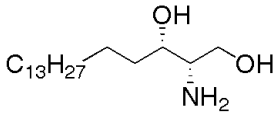
A short and efficient synthesis of (2*S*,3*S*)-safingol from commercially available D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine is described. The highlights of the synthesis are a stereoselective one-pot transformation of a diol into an epoxide under phase transfer catalytic conditions and a regioselective epoxide-opening reduction with a hydride reagent.

Key Words: Safingol, Phytosphingosine, Phase transfer catalysis, Epoxide-forming reaction, Reduction

Introduction

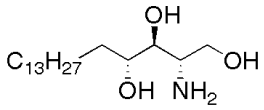
Safingol (**1**), (2*S*,3*S*)-2-aminooctadecane-1,3-diol, an antineoplastic and antipsoriatic drug,[1] has been extensively investigated for its role in cell regulation, signal transduction,[2] and inhibition of protein kinase C.[3] Furthermore, safingol enhances the cytotoxic effect of the chemotherapeutic agent mytomycin C by promoting drug-induced apoptosis.[4] The effects of doxorubicin are also potentiated by co-administration of safingol.[5]



Safingol (**1**)

There are two general synthetic routes to safingol (**1**) reported in the literature, diastereoselective or enantioselective methods[6a-e] and practical resolution methods of racemic mixtures.[7] Examples of stereoselective syntheses include: enantioselective Henry reaction[6a] of hexadecanal, followed by hydrogenation; an eight-step synthesis involving asymmetric borane reduction of a ketone moiety[6b] as a key step; stereoselective reduction of a chiral 2-acylaziridine intermediate;[6c] total synthesis starting from (*Z*)-but-2-ene-1, 4-diol;[6d] and diastereoselective synthesis *via* nucleophilic addition to a chiral oxazolidinyl ester.[6e] Most recently, safingol was prepared from protected glyceraldehydes,[8] a *trans*-oxazoline derivative,[9] and D-glycal[10] through carbon chain extension strategies and efficient one-pot catalytic reduction of multifunctional groups. Most of the above-mentioned syntheses involve either multi-step reactions, including preparation steps for chiral ligands or auxiliaries, or generation of undesired stereoisomers. Our strategy is focused on efficient synthesis of an optically pure safingol by short reaction steps from D-*ribo*-(2*S*,3*S*,4*R*)-phytosphingosine.

As a starting material, phytosphingosine is a recently commercially available and inexpensive compound suitable for facile preparation of optically pure safingol without elaboration of the carbon chain backbone and with stereocontrol at C-2 position. This is the first example of a synthesis of safingol using phytosphingosine as a starting material as well as the shortest step synthesis for optically pure safingol among published synthetic methods.

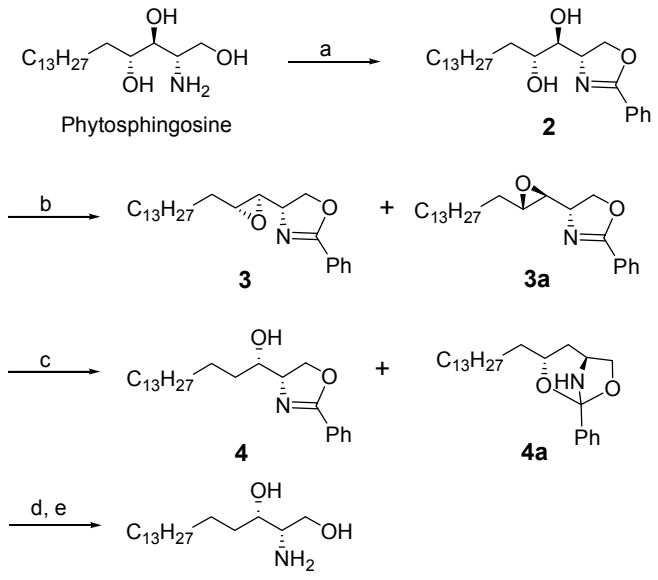


Phytosphingosine

Results and Discussion

The present work is outlined in Scheme 1.

Compound **2** was obtained by a literature procedure[11] whereby treatment of phytosphingosine with ethyl benzimidate hydrochloride regioselectively produced protected diol **2**, possessing an oxazoline moiety at the 1,2-position, in



Scheme 1. Synthesis of safingol **1**. Reagents and conditions: (a) PhC(NH)OEt·HCl, Et_3N, CH_2Cl_2, reflux, 72 h, 91%; (b) TsCl, NaOH, TBAI, THF, 19 h, 71% (**3**), 10% (**3a**); (c) L-selectride (4 equiv), THF, -10 °C to RT, 10 h, 80% (**4**), 3% (**4a**); (d) 2 M HCl, THF, 4 h; (e) 12.5 M NaOH, MeOH, reflux, 40 min, 78%.

excellent yield. This procedure effectively avoids several tedious protecting steps necessary to prepare the safingol precursor. In addition, the oxazoline group is expected to be stable under subsequent synthetic steps requiring strong, basic conditions.

The next step to retain the stereochemistry of **1** is to substitute the 4-hydroxyl group with hydrogen and invert the configuration of the 3-hydroxyl group of protected diol **2**. Epoxide **3** can fulfill this strategy as it can be converted to safingol precursor **4** after the epoxide-opening reaction at the less sterically hindered 4-position with an appropriate hydride donor.

At the current stage, either tosylation or mesylation of **2**, followed by intramolecular nucleophilic substitution by the adjacent hydroxyl group generally affords the (3*S*,4*S*)-epoxide **3a** as a major product in *ca*. 70% overall yield, instead of the desired (3*R*,4*R*)-epoxide **3**. It is a well-known, two-step method to generate epoxide functionality in the field of phytosphingosine chemistry.[11,12] Therefore, the stereoselective transformation of diol **2** into the (3*R*,4*R*)-epoxide **3**, one of the key intermediates, is required for efficient synthesis of **1**. Main strategy for the diastereoselective formation of **3** is to produce the kinetically-favored alkoxide ion through the 5-membered ring chelation (**A**) between the lithium cation and sp^2-nitrogen, instead of the 6-membered ring chelation (**B**) resulting from deprotonation at the 4-hydroxyl group as shown in Fig. 1. A generation of this alkoxide ion intermediate under strong, basic condition facilitates introduction of leaving group at the 3-position of **2**, and subsequent nucleophilic substitution with inversion of configuration at this position, providing required epoxide **3**.

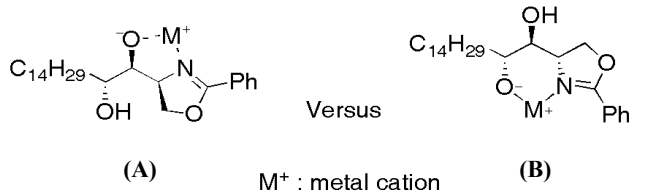
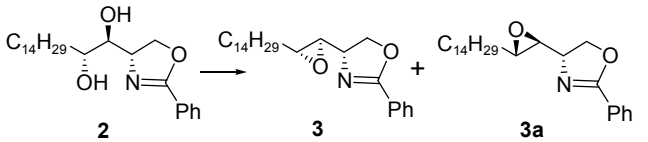


Figure 1. The chelation modes between M^+ and the sp^2-nitrogen of diol **2**.

Table 1. Stereoselective transformation reactions of diol **2** to epoxide **3**.



Entry	Reagent (equiv)	Base (equiv)	Solvent	Catalyst	Ratio **3**:**3a**[a]	Yield (**3**, %)[b]
1	SDI (1.1)	*t*-BuLi (2.2)	THF	-	5:1	54
2	TsCl (3.2)	50% aq NaOH[c]	CH_2Cl_2/ H_2O[c]	BTAB	4.5:1	55
3	TsCl (2.2)	NaOH (6.0)	CH_2Cl_2	TBAI	10:6[d,e]	50[e]
4	TsCl (2.2)	NaOH (6.0)	THF	TBAI	7:1	71

[a]Average ratio determined by ^{1}H-NMR analysis. [b]Isolated yield of **3** after purification by column chromatography. [c]Szeja's reaction condition: excess of 50% aqueous NaOH was used. [d]Ratio of **3** and the epoxide-opened side product induced by the dichloromethanide anion as an inseparable mixture. [e]Yield calculated by ^{1}H-NMR spectroscopy.
SDI = 1,1′-sulfonyldiimidazole; TsCl = *p*-toluenesulfonyl chloride; BTAB = benzyltriethylammonium bromide; TBAI = tetrabutylammonium iodide.

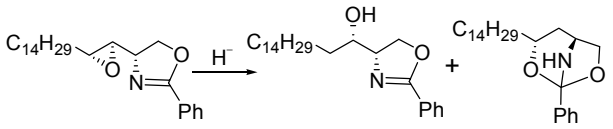
One such transformation began with the reaction of **2** with 1,1′-sulfonyldiimidazole/*t*-butyllithium.[13a,b] It provided epoxide **3** and the diastereomer **3a** in a respective ratio of 5:1 and an isolated yield of 54% for **3** (Table 1, entry 1). The most difficult issue to overcome was the selection of the solvent systems for chromatography in order to separate **3** from **3a**. We found chloroform:ethyl acetate (10:1, v/v) to be the appropriate solvent system.

Another one-pot transformation of **2** into **3** utilizes *p*-toluenesulfonyl chloride in CH_2Cl_2/NaOH (aq) under liquid-liquid phase transfer catalytic (PTC) conditions. These conditions originated from Szeja's procedure[14] that involve the functional group transformation of simple cyclic or acyclic diols into corresponding epoxides (Table 1, entry 2). In the cases of the PTC reactions applying Szeja's procedure, aqueous NaOH seems not only to hydrolyze *p*-toluenesulfonyl chloride but also to produce a large amount (24% yield) of the side product tosylated at both the 3- and 4-positons of **2**. To overcome such obstacles, a solid-liquid PTC reaction in CH_2Cl_2 was explored, as shown in Table 1. Unfortunately, this generated a considerable amount of an inseparable epoxide ring-opened side product derived from the further reaction between **3** and the dichloromethanide anion. Due to formation of this ring-opened side product, the reaction resulted in a lower diastereoselectivity and yield of **3** than those of the liquid-liquid PTC reaction (Table 1, entry 3). The modified process to minimize the aforementioned problems was to treat **2** with both powdered NaOH and THF, as the base and solvent, under solid-liquid PTC conditions. Application of this procedure led to superior diastereoselectivity (7:1) between **3** and **3a** and an enhanced yield (71%) of **3** as compared with the other results in Table 1 (entry 4). The good stereoselectivity can be also suggested by the above chelation model which is replaced lithium cation with quaternary ammonium ion. In this case, molecular model of the chelation mode (B) shows much severer steric hindrance between long chain alkyl group and butyl group of catalyst than that of the chelation mode (A). Therefore, the quaternary ammonium ion can facilitate to form a 5-membered ring chelated complex more readily than 6-membered ring complex. In addition, this modified PTC reaction furnished the least amount of side products in contrast with the other three epoxide-forming reactions. Consequently, it was the most promising reaction to generate epoxide **3** from diol **2** in a single step.

The second key intermediate, **4**, was prepared from an epoxide-opening reduction of **3** with a wide range of hydride nucleophiles with their results summarized in Table 2.

Nucleophilic ring-opening reductions of the epoxide groups

Table 2. Reduction of 3 with typical hydride reagents.[a]



3 **4** **4a**

Entry	Reducing agent	Equivalent	Ratio **4**:**4a**[b]	Yield (**4**, %)[c]
1	$LiBH_4$	4.0	NR[d]	-
2	Red-Al®	4.0	NR	-
3	$(i\text{-Bu})_2AlH$	3.0	NR	-
4	$LiAlH_4$	1.1 ~ 2.4	2:1 ~ 1:2[e]	≤ 40
5	$Li(Et)_3BH$	4.0	7:3	61
6	$Li(sec\text{-Bu})_3BH$	4.0	26:1	80

[a]Reductions carried out in THF from −15 °C to RT. [b]Average ratio observed by proton NMR spectroscopy. [c]Isolated yield of **4** after purification by recrystallization in methanol. [d]No reaction occurred. [e]Variable ratio according to the equivalents of $LiAlH_4$ used. Red-Al® = sodium bis-(2-methoxyethoxy)aluminum hydride. The average ratio determined by ^{1}H-NMR analysis.

in phytosphingosine derivatives are believed to occur regioselectively from preferential attack of hydride species at the less sterically hindered C-4 position.[15a-c] However, depending on nature of the hydride reagent, reduction of epoxide **3** to form corresponding alcohol **4** did not show a similar tendency toward previous cases. Epoxide **3** was resistant to reductions with both lithium borohydride and Red-Al® [sodium bis(2-methoxyethoxy) aluminum hydride], possibly as a result of the lower reducing power of $LiBH_4$ and steric hindrance of Red-Al® (Table 2, entries 1 and 2). In particular, unsuccessful DIBAL-H (diisobutylaluminum hydride) reduction of **3** was an exceptional case, because reductions with DIBAL-H have been reliably achieved with most of the epoxides.[15b,c] Probably, reduction does not work as the second equivalent of DIBAL-H is unable to approach the C-4 position due to severe steric hindrance caused by a tight coordination of neutral DIBAL-H to the sp^2-nitrogen of **3** (Table 2, entry 3). Thus, a series of other hydride reagents were examined. In the case of $LiAlH_4$, the ratio of **4**:**4a** varied from 2:1 to 1:2, with **4** decreasing as the amount of reducing agent was increased to complete the reaction. Side product **4a** is inevitably formed while the reduction of **3** works well with the hydride nucleophile. The side reaction proceeds *via* nucleophilic attack of a C-4 alkoxide ion generated *in situ* at a reduction stage to an electrophilic site in the oxazoline moiety, leading directly to cyclization of the intermediate (Table 2, entry 4). The structure of **4a** was verified by COSY experiments and mass spectrometry, although it was a mixture with **4**. Alcohol **4** was isolated from **4a** after purification by recrystallization in methanol. These mixtures were not able to be separated by column chromatography due to their same polarities in any solvents. Conversely, super-hydride (lithium triethylborohydride) reduction[16] gave alcohol **4** as the major product with better regioselectivity (*ca*. 7:3) and a higher yield (61%) than those of $LiAlH_4$ reduction (Table 2, entry 5). Surprisingly, the best result came from L-selectride [lithium tri(*sec*-butyl)-borohydride] reduction, exhibiting an excellent regioselectivity of 26:1 (**4**:**4a**), together with an optimum yield of 80% (Table 2, entry 6). L-Selectride is often a more regioselective reducing agent than super-hydride, displaying both superior regioselectivity and better yield.[17] It proved to be the most useful and regioselective reducing agent as well among the hydride reagents used in the epoxide-opening reaction of **3**. The use of 4.0 equivalents of L-selectride was a critical factor to complete the reduction and to achieve optimum yield.

Finally, the deprotection reaction of **4** in acidic medium followed by basic hydrolysis gave the optically pure safingol (**1**) in 78% yield after either washing the reaction residue with $CHCl_3$ or purification by column chromatography (chloroform: methanol:ammonia (aq), 60:10:4). All the spectral data of the final compound prepared were identical with the reference data of safingol (**1**).[6a,7] This has been the shortest step synthesis for optically pure safingol since its synthetic procedures were first published.

Conclusion

Herein, this synthesis of safingol (**1**) is first to be achieved efficiently from commercially available phytosphingosine in just over five steps and a 40% overall yield. The key steps were the stereoselective one-pot transformation of diol **2** into epoxide **3** under PTC conditions and the regioselective ring-opening reduction of epoxide **3** with L-selectride.

Experimental Section

General methods. All reactions were carried out under nitrogen atmosphere. D-*ribo*-(2*S*,3*S*,4*R*)-Phytosphingosine was obtained from Doosan Biotech BU (JP Chem), Korea. Tetrahydrofuran was freshly distilled immediately before use. Other solvents were dried over either $MgSO_4$ or Na_2SO_4 before use. All other reagents were purchased from commercial sources and used without further purification, unless specifically stated.

All reactions were monitored by thin layer chromatography with Merck silica gel 60 F_{254}. Flash chromatography was performed on Merck Kiesegel 60 flash silica gel (E. Merck, Art 7734, 70 - 230 mesh). Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker, Avance 600 spectrometer or a Bruker, Avance 500, as noted in the experimental for each compound. Chemical shifts are reported relative to the residue peaks of the solvent ($CDCl_3$: 7.26 ppm for ^{1}H and 77.0 ppm for ^{13}C), (CD_3OD: 3.3 ppm for ^{1}H and 49.0 ppm for ^{13}C). The following abbreviations are used to denote the multiplicities: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, br = broad and m = multiplet. Diastereomeric ratios were determined by ^{1}H NMR (600 MHz) analyses of the mixtures isolated by column chromatography. Melting points were obtained using a Stuart SMP3 (Barloworld scientific Ltd.) and are uncorrected. Infrared spectra were recorded by the KBr pellet method on a Perkin Elmer spectrum 100 in range of 4000-400 cm^{-1}. Optical rotations were recorded on an AUTOPOL III digital

polarimeter at 546 nm and reported as follows: concentration (*c* in g/100 mL) and solvent. High resolution mass-spectra were obtained on a JEOL JMS600 spectrometer at Mass Spectrometry Laboratory in Seoul National University.

2-Phenyl-(4*S*)-[(1*S*,2*R*)-1,2-dihydroxyhexadecyl]-1,3-oxazoline (2). To a stirred suspension of D-*ribo*-(2*S*, 3*S*, 4*R*)-phytosphingosine (6.01 g, 18.9 mmol) and ethyl benzimidate hydrochloride (4.22 g, 22.7 mmol) in dichloromethane (135 mL) was added triethylamine (3.20 mL, 22.7 mmol). The reaction mixture was stirred for 72 h at 40 °C and cooled to room temperature. The insoluble product was filtered and recrystallized from methanol to give diol **2** (6.95 g, 91%) as a white crystal.

R_f: 0.58 (chloroform:methanol, 9:1); mp 137-139 °C, lit[11] 137-138 °C; [α] 30.6 (*c* 0.22, $CHCl_3$:CH_3OH, 5:1, v/v), lit[11] [α] 24.8 (*c* 1.60, $CHCl_3$:CH_3OH, 5:1, v/v); IR (thin film, KBr): 3325, 3071, 2954, 2922, 2851, 1645, 1604, 1582, 1499, 1468 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.95-7.86 (d, 2H, *J* = 7.4 Hz, Ph), 7.50-7.43 (m, 1H, Ph), 7.43-7.35 (m, 2H, Ph), 4.60-4.50 (m, 1H), 4.50-4.45 (m, 1H), 4.45-4.37 (m, 1H), 3.87-3.80 (m, 1H), 3.75-3.68 (t, 1H, *J* = 5.8 Hz, H_3), 3.28-3.20 (brs, 1H, OH), 2.28-2.10 (brs, 1H, OH), 1.75-1.65 (m, 1H, H_5), 1.54-1.45 (m, 1H, $H_{5'}$), 1.45-1.18 (m, 24H, $(CH_2)_{12}$), 0.91-0.85 (t, 3H, *J* = 6.7 Hz, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.6, 131.9, 128.6, 127.4, 75.9, 74.2, 70.2, 69.6, 33.2, 32.1, 29.9, 29.9, 29.8, 29.6, 25.6, 22.9, 14.3 ppm; HRMS (FAB^+) calculated for $C_{25}H_{42}O_3N$, 404.3165 $[M+1]^+$ *m/z*; observed, 404.3164 $[M+1]^+$ *m/z*.

2-Phenyl-(4*S*)-[(1*R*,2*R*)-1,2-epoxyhexadecyl]-1,3-oxazoline (3). To a mixture of diol **2** (5.00 g, 12.4 mmol), tetrabutylammonium iodide (234 mg, 0.62 mmol) and NaOH (4.96 g, 124 mmol) in THF (140 mL), was added *p*-toluenesulfonyl chloride (2.627 g, 13.8 mmol). The reaction mixture was stirred for 10 h. *p*-Toluenesulfonyl chloride (2.627 g, 13.8 mmol) in dichloromethane (20 mL) was then added to the reaction mixture and the resulting mixture stirred for an additional 9 h. The insoluble residue was removed from the reaction mixture by filtration. The solution was diluted with dichloromethane (300 mL) and the dichloromethane washed with water (100 mL). The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by flash column chromatography (chloroform:ethyl acetate, 40:1 to 10:1) to give epoxide **3** (3.40 g, 71%) and **3a** (0.48 g, 10%) as a white powder.

R_f: 0.60 (chloroform:ethyl acetate, 10:1); mp 63-65 °C; [α] 94.1 (*c* 1.01, $CHCl_3$); IR (thin film, KBr): 2957, 2918, 2851, 1655, 1640, 1579, 1495, 1471, 1450 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.98-7.91 (d, 2H, *J* = 7.2 Hz, Ph), 7.51-7.45 (m, 1H, Ph), 7.44-7.37 (m, 2H, Ph), 4.54-4.43 (m, 2H, $H_{1'}$ and H_2), 4.31-4.24 (m, 1H, H_1), 3.09-3.02 (td, 1H, *J* = 5.7 and 1.8 Hz, H_4), 2.99-2.92 (m, 1H, H_3), 1.60-1.53 (m, 1H, H_5), 1.50-1.36 (m, 1H, $H_{5'}$), 1.36-1.19 (m, 24H, $(CH_2)_{12}$), 0.91-0.85 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR (126 MHz, $CDCl_3$): δ 165.4, 131.7, 128.6, 128.5, 127.7, 69.2, 66.6, 59.4, 56.0, 32.1, 31.9, 29.9, 29.9, 29.9, 29.8, 29.8, 29.7, 29.6, 29.6, 26.2, 22.9, 14.3 ppm; HRMS (FAB^+) calculated for $C_{25}H_{40}O_2N$, 386.3059 $[M+1]^+$ *m/z*; observed, 386.3057 $[M+1]^+$ *m/z*.

2-Phenyl-(4*S*)-[(1*S*,2*S*)-1,2-epoxyhexadecyl]-1,3-oxazoline (3a). R_f: 0.68 (chloroform:ethyl acetate, 10:1); mp 70-73 °C, lit[11] 63-64 °C; [α] 45.8 (*c* 1.04, $CHCl_3$), lit[11] [α] 24.8 (*c* 1.60, $CHCl_3$:CH_3OH, 5:1, v/v); IR (thin film, KBr): 2957, 2918, 2851, 1655, 1640, 1579, 1495, 1471, 1450 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.99-7.93 (d, 2H, *J* = 7.8 Hz, Ph), 7.52-7.47 (m, 1H, Ph), 7.45-7.38 (m, 2H, Ph), 4.51-4.44 (m, 1H, $H_{1'}$), 4.36-4.30 (t, *J* = 7.8 Hz, 1H, H_1), 4.24-4.16 (m, 1H, H_2), 2.96-2.91 (m, 1H, H_4), 2.90-2.85 (dd, 1H, $J_{2,3}$ = 6.0 Hz, $J_{3,4}$ = 1.8 Hz, H_3), 1.69-1.63 (m, 1H, H_5), 1.59-1.51 (m, 1H, $H_{5'}$), 1.41-1.19 (m, 24H, $(CH_2)_{12}$), 0.90-0.85 (t, 3H, *J* = 6.6 Hz, CH_3) ppm.

2-Phenyl-(4*S*)-[(1*S*)-1-hydroxyhexadecyl]-1,3-oxazoline (4). To a solution of epoxide **3** (1.00 g, 2.602 mmol) in THF (50 mL) was added L-selectride (1.0 M in THF, 10.4 mL, 10.4 mmol) at –10°C. The reaction mixture was stirred for 7 h at this temperature and maintained at RT for additional 3 h. The reaction was quenched with aqueous NaOH solution (20 mL). The resulting solution was diluted with dichloromethane (100 mL) and the dichloromethane washed with water (50 mL), dried ($MgSO_4$) and evaporated *in vacuo*. The residue was filtered through a silica gel eluted with ethyl acetate and the filtrate was concentrated *in vacuo*. The resulting residue was washed with methanol (25 mL) to remove **4a** and to give alcohol **4** (0.81 g, 80%) as a white crystal.

R_f: 0.37 (chloroform:ethyl acetate, 10:1); mp 114-115°C; [α] 73.0 (*c* 1.02, $CHCl_3$); IR (thin film, KBr): 3163, 2929, 2850, 1643, 1469, 1455, 1381 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.98-7.92 (d, 2H, *J* = 7.8 Hz, Ph), 7.52-7.45 (m, 1H, Ph), 7.45-7.37 (m, 2H, Ph), 4.53-4.44 (m, 1H, $H_{1'}$), 4.29-4.22 (m, 1H, H_2), 4.22-4.15 (m, 1H, H_1), 3.55-3.47 (m, 1H, H_3), 2.31-2.23 (d, 1H, *J* = 5.4 Hz, OH), 1.58-1.48 (m, 2H), 1.48-1.17 (m, 26H, $(CH_2)_{13}$), 0.92-0.83 (t, 3H, ^3J = 6.6 Hz, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ 165.0, 131.6, 128.4, 128.4, 127.4, 74.2, 71.6, 69.8, 34.2, 31.9, 29.7, 29.7, 29.6, 29.6, 29.4, 25.8, 22.7, 14.1 ppm; HRMS (CI^+) calculated for $C_{25}H_{42}O_2N$, 388.3215 $[M+1]^+$ *m/z*; observed, 388.3213 $[M+1]^+$ *m/z*.

(1*R*,3*R*,4*S*,5*S*)-1-Phenyl-3-tetradecyl-2,7,8-dioxazabicyclo-[3.2.1]octan-4-ol (4a, a mixture with 4). R_f: 0.37 (chloroform:ethyl acetate, 10:1); ^1H NMR (600 MHz, $CDCl_3$): δ 7.93-7.89 (d, 2H, *J* = 7.8 Hz, Ph), 7.55-7.46 (m, 1H, Ph), 7.42-7.37 (m, 2H, Ph), 4.89-4.85 (s, 1H, NH), 4.63-4.57 (dd, 1H, *J* = 9.6 and 8.7 Hz, H_1), 4.48-4.41 (m, 1H, H_2), 4.03-3.96 (m, 2H, $H_{1'}$ and H_4), 1.88-1.82 (ddd, 1H, *J* = 13.5, 3.6 and 1.2 Hz, H_3), 1.63-1.50 (m, 2H, $H_{3'}$ and $H_{5'}$), 1.50-1.40 (m, 1H, H_5), 1.40-1.20 (m, 24H, $(CH_2)_{12}$), 0.90-0.85 (t, 3H, *J* = 6.6 Hz, CH_3); ^{13}C NMR (151 MHz, $CDCl_3$): δ 163.8, 131.7, 128.3, 127.1, 73.3, 71.8, 66.7, 43.1, 37.6, 31.9, 29.7, 29.7, 29.4, 25.5, 22.7, 14.1 ppm; MS (FAB^+): *m/z* (%): 388 (100) $[M+1]^+$, 105 (53).

(2*S*,3*S*)-2-Aminooctadecane-1,3-diol (safingol, 1). To a solution of alcohol **4** (178 mg, 0.460 mmol) in THF (10 mL) was added aqueous HCl (2 M, 2.5 mL). The reaction mixture was stirred for 4 h and the solvents were evaporated *in vacuo*. The resulting residue was used for next reaction without further purification. The residue was dissolved in methanol (10 mL)/aqueous NaOH (12.5 M, 4.2 mL) and the reaction mixture refluxed for 40 min. The solvents were concentrated

in vacuo and the residue partitioned into dichloromethane (50 mL) and water (10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by either washing it with chloroform (10 mL) or flash column chromatography (chloroform:methanol:ammonia (aq.), 40:1:0 to 6:1:0.4) to give safingol **1** (108 mg, 78%).

R_f: 0.06 (chloroform:methanol, 5:1); mp 109-110 °C, lit[7] 107-109 °C; [α] –11.2 (*c* 0.10, $CHCl_3$:CH_3OH, 10:1, v/v), lit[6a] $[\alpha]_D$ –11.05 (*c* 0.29, $CHCl_3$:CH_3OH, 10:1, v/v, 97% ee); IR (thin film, KBr) 3365, 3314, 2955, 2918, 2852, 1579, 1468 m^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ 3.64-3.56 (dd, 1H, $J_{1,1'}$ = 10.8 Hz, $J_{1,2}$ = 4.8 Hz, H_1), 3.56-3.49 (m, 1H, H_3), 3.49-3.43 (dd, 1H, $J_{1',2}$ = 6.6 Hz, $H_{1'}$), 2.68-2.59 (m, 1H, H_2), 1.40-1.20 (m, 28H, $(CH_2)_{14}$), 0.91-0.85 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR (151 MHz, CD_3OD): δ 72.7, 65.0, 58.0, 35.0, 33.2, 31.0, 27.1, 23.9, 14.6 ppm; HRMS (CI^+) calculated for $C_{18}H_{40}O_2N$, 302.3059 $[M+1]^+$ *m/z*; observed, 302.3058 $[M+1]^+$ *m/z*.

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