Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis of Amphiphilic Amino Alcohols

Lauri Toom [a], Piret Villo [a], Ilme Liblikas [a] & Lauri Vares [a]
[a] University of Tartu, Institute of Technology, Tartu, Estonia
Published online: 31 Oct 2008.

To cite this article: Lauri Toom, Piret Villo, Ilme Liblikas & Lauri Vares (2008) Synthesis of Amphiphilic Amino Alcohols, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:23, 4295-4313, DOI: 10.1080/00397910802326554

To link to this article: http://dx.doi.org/10.1080/00397910802326554

Synthetic Communications®, 38: 4295–4313, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802326554

Taylor & Francis
Taylor & Francis Group

Synthesis of Amphiphilic Amino Alcohols

Lauri Toom, Piret Villo, Ilme Liblikas, and Lauri Vares
University of Tartu, Institute of Technology, Tartu, Estonia

Abstract: An efficient and general approach for the synthesis of amphiphilic 1,2-amino alcohols is reported. The use of *N*-benzyl protecting groups is essential for obtaining good yields when opening a long-chain terminal epoxide with an amine.

Keywords: Amino alcohols, amphiphiles, epoxide opening, *N*-benzyl protecting group

INTRODUCTION

The 1,2-amino alcohol moiety is a common structural fragment in many biologically active natural and synthetic compounds, as well as in auxiliaries and ligands for asymmetric synthesis.[1] Amphiphilic amino alcohols are compounds in which the amino alcohol moiety is linked to one or two aliphatic alkyl chains.[2] In recent decades, this class of compounds have been extensively studied because of their interesting applications, some examples being surfactants,[3] antimicrobial agents,[4] and potential ionophores.[5] For example, ethambutol **1** is a bacteriostatic antimycobacterial front-line agent that is recommended by the World Health Organization for the treatment of tuberculosis (Fig. 1).[6] Several promising analogs of ethambutol have been synthesized in recent years.[7,8] In this respect, Tripathi and coworkers synthesized a series of glycosyl amino alcohols having alkyl chains of varying lengths (e.g., **2a** and **2b**)[8] and found that compound **2a** is, in vitro, superior to ethambutol.[9] In addition, similar structural motifs have been used as main structural fragments

Received May 5, 2008.
Address correspondence to Lauri Vares, University of Tartu, Institute of Technology, 1 Nooruse Street, 50411 Tartu, Estonia. E-mail: lauri.vares@ut.ee

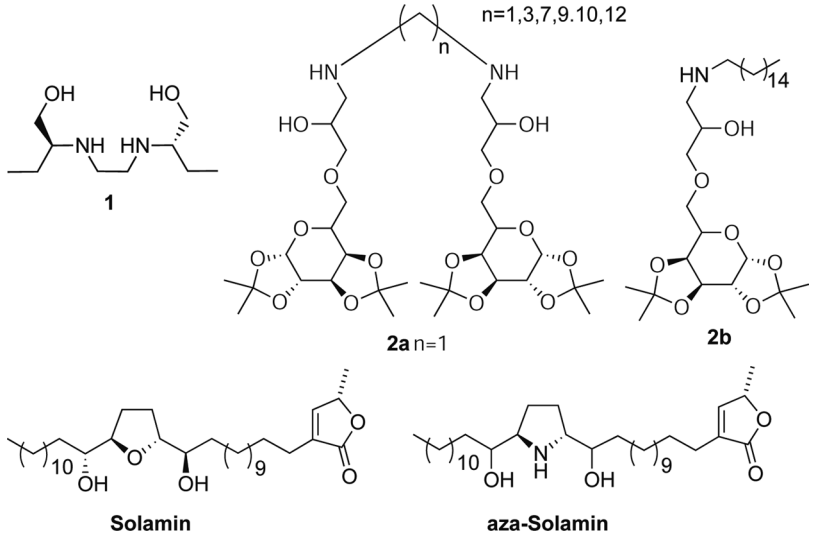


Figure 1. Ethambutol **1** and glycosyl amino alcohols **2a** and **2b** as antituberculosis agents: acetogenin solamin and synthetic aza-solamin.

in carbohydrate-based surfactants.[10] Acetogenins, a type of compounds isolated from the plant family *Annonaceae*, constitute a novel class of very promising anticancer agents (e.g., solamin in Fig. 1).[11] Recently a few studies of acetogenin aza-analogs have been published containing the amino alcohol structural motif, one example being aza-solamin.[12]

As a part of an ongoing investigation we became interested in amino alcohols that are structurally related to acetogenins and aza-acetogenins having the generic structures **3** and **4** (Fig. 2). These compounds have a polar amino alcohol head group, containing either one or two amine functionalities, and two lipophilic tail groups. For the preparation of this type of vicinal amino alcohol moieties, ringopening of epoxides has been one of the main methods of choice,[13] and this is perhaps a result of the

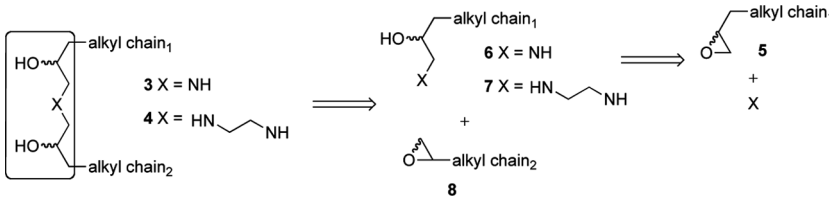


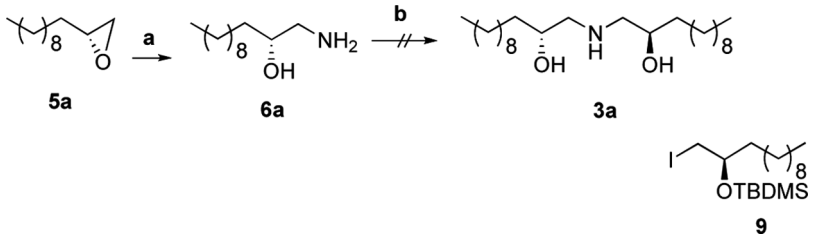
Figure 2. General synthetic route to amhiphilic amino alcohols.

plethora of asymmetric methods available for the synthesis of epoxides from olefins.[14] However, depending on the specific amine and epoxide that are to be coupled, these ringopening reactions can be sluggish, requiring dry reaction conditions (in the case of Lewis acid activation) or afford the product in impractically low yields.[15] The reasons for the observed low reactivity are not always obvious, making it difficult to predict the outcome of these reactions. Herein we report a general synthesis of amphiphilic amino alcohols having the generic structures **3** and **4** via an epoxide opening strategy, thus providing a general solution to the problem discussed previously.

According to our general synthetic approach, both lipophilic tails are introduced as epoxides (Fig. 2). Epoxide **5** is first opened with either ammonia or ethylene-1,2-diamine, yielding amino alcohol **6** or **7**, respectively. Epoxide **8** is then opened with intermediate **6** or **7** to yield the desired product **3** or **4**, respectively. The use of enantiomerically pure epoxides gives an entry to asymmetrically defined products. Epoxides **5** and **8** can be prepared with high enantiomeric purity by a Sharpless asymmetric dihydroxylation of the corresponding olefin followed by cyclization, for example.[14]

RESULTS AND DISCUSSION

Epoxide **5a**, prepared from 1-dodecene via an asymmetric dihydroxylation,[16] tosylation,[17] and epoxidation sequence, was conveniently opened with ammonia to afford amino alcohol **6a**[18] in 99% yield (Scheme 1). Coupling of amine **6a** with a second equivalent of epoxide **5a** was surprisingly sluggish. Refluxing in 2-PrOH for 1 week afforded at best only trace amounts of the desired compound **3a** (Table 1, entry 1). Using 1,4-dioxane as solvent and thereby increasing the reaction temperature did not improve the conversion (entry 2). Attempts to



Scheme 1. (a) Ammonium hydroxide (excess), EtOH, 60 °C, 16 h, 99%; (b) **5b** or **9**, for reaction conditions, see text and Table 1 (entries 1–6).

Table 1. *N*-Alkylation of amino alcohols with epoxides

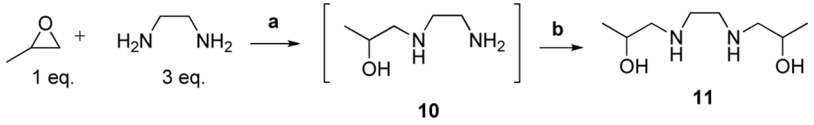
Entry	Amino alcohol	Epoxide	Product	Reaction conditions	Yield (%)
1	**6a**	**5a**	**3a**	2-PrOH, reflux, 1 week	Traces
2	**6a**	**5a**	**3a**	1,4-dioxane, reflux, 1 week	Traces
3	**6a**	**5a**	**3a**	cat. $CoCl_2$, MeCN, rt up to 70 °C	ncd[b]
4	**6a**	**5a**	**3a**	cat. $FeSO_4$, MeCN, rt up to 70 °C	ncd[b]
5	**6a**	**5a**	**3a**	cat. CF_3SO_3H, MeCN, rt up to 60 °C	ncd[b]
6	**6a**	**5a**	**3a**	0.1 eq K_2CO_3, 0.1 eq TEBA, dioxane, 90 °C, 6 days	ncd[b]
7	**6b**	**5b**	**3b**	2-PrOH, reflux, 4 days	ncd[b]
8	**6b**	**5b**	**3b**	0.1 eq K_2CO_3, 0.1 eq TEBA, dioxane, 90 °C, 7 days	53[a]
9	**6c**	**5b**	**3c**	0.1 eq K_2CO_3, 0.1 eq TEBA, dioxane, 90 °C, 10 days	54[a]
10	**6d**	**5b**	**3d**	2-PrOH, reflux, 48 h	87[a]
11	**7b**	**5a**	**4b**	2-PrOH, reflux, 24 h	74[a]
12	**7a**	**5a**	**4a**	2-PrOH, reflux, one week	ncd[b]

[a]Isolated yield.
[b]Ncd—no conversion detected.

activate the epoxide with Lewis acids ($CoCl_2$, $FeSO_4$) or a Brønsted acid (CF_3SO_3H) proved fruitless (entries 3–5). We tested solid–liquid phase-transfer conditions[19] (entry 6) but did not observe any conversion after 6 days at 90 °C. We then prepared iodide **9** from (*R*)-dodecane-1,2-diol and attempted to couple it with the left-hand fragment **6a** but, however, once again the coupling failed. We were surprised and puzzled by the low reactivity of **6a**, especially taking into account that the coupling between **5a** and ammonia proceeded smoothly.

Compound **6a** has a lipophilic tail connected with a polar head group. We speculated that this might cause a micelle formation, which in turn slows down the desired coupling reaction. To test our hypothesis, we reacted propylene oxide with 3 eq. of ethylene-1,2-diamine (Scheme 2). The intermediate **10** is lacking the lipophilic alkyl chain and its subsequent reaction with propylene oxide proceeded smoothly to form **11** (Scheme 2). However, when propylene oxide was reacted with **6a** under the same reaction conditions, no reaction took place.

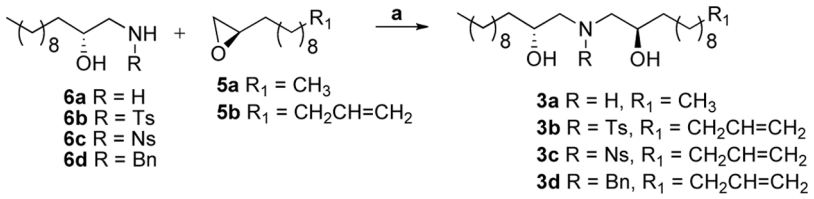
Consequently, reducing the polarity of the head group in compound **6** should also reduce its propensity for forming micelles and, as a result,



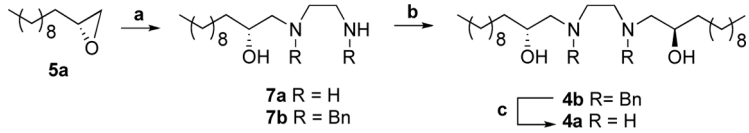
Scheme 2. (a) MeCN, 65 °C, 24 h, 68%; (b) propylene oxide (3 eq.), MeCN, 65 °C, 24 h, 87%.

increase its reactivity in the subsequent coupling reaction. To test this, compounds **6b**, **6c**, and **6d** were prepared from tosylamide, nosylamide[20], and benzylamine, respectively (Scheme 3). Epoxides **5a** and **5b** were used as electrophiles. Epoxide **5b** was prepared from 1,13-tetradecadiene and has a terminal olefin as a handle for further functionalization of **3**. When tosylamide **6b** and epoxide **5a** were refluxed in 2-PrOH, no conversion was detected after 4 days (Table 1, entry 7). Coupling of **6b** with epoxide **5b** gave 53% yield of compound **3b** after heating the reaction mixture for 1 week in dioxane at solid–liquid phase-transfer conditions[19] (Table 1, entry 8). When **6c** was used instead, the coupling with **5b** afforded **3c** in 54% yield using the same solid–liquid phase-transfer conditions (Table 1, entry 9). However, when reacting **6d** with **5b**, the desired coupling product **3d** was obtained in 87% yield after only 48 h (entry 10), clearly demonstrating the usefulness of this method.

After having identified a suitable protocol for the coupling of the left- and right-hand fragments with an amine core, we tested the generality of this strategy by preparing a similar compound having an ethylene-1,2-diamine core (Scheme 4, and Scheme 5). Epoxide **5a** was smoothly opened with *N*,*N*′-dibenzylethylene-1,2-diamine to afford amine **7b**. When **7b** was treated with epoxide **5a**, the desired product **4b** was formed in 74% yield (Table 1, entry 11). However, as could be predicted, amino alcohol **7a** did not react with epoxide **5a** (entry 12). It was also shown that the benzyl groups in compound **7b** could be efficiently removed by using a standard hydrogenolysis protocol to afford the amphiphilic amino alcohol **4a**.



Scheme 3. (a) *N*-Alkylation of amino alcohols with epoxides. For reaction conditions, see Table 1.

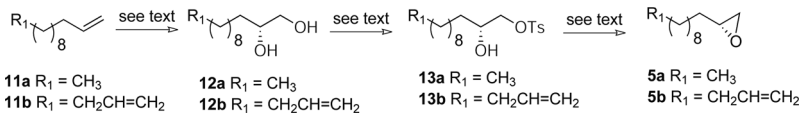


Scheme 4. (a) 2-PrOH, reflux, 24 h, 99% (**7a**), 81% (**7b**); (b) see Table 1, entries 11 and 12; (c) cat. Pd/C, H_2 (1 atm), MeOH, 14 h, 82%.

Herein we have demonstrated a simple and convenient method for the synthesis of amphiphilic 1,2-amino alcohols and showed that the use of *N*-benzyl protecting groups is essential for obtaining good yields when opening a long-chain terminal epoxide with an amphiphilic amine.

EXPERIMENTAL

All commercially available chemicals were of reagent grade and used without further purification; solvents used for high-performance liquid chromatography (HPLC) analysis were of anatytical grade. Epoxides **5a** and **5b** were prepared according to Scheme 5. Enantiomeric ratio of **15a** and **15b** was 92:8, determined by chiral gas chromatography (GC) analyses. Flash-column chromatography was performed on silica gel (Merck, Kieselgel 60, 230–400 mesh). NMR spectra were obtained on a Bruker Avance-II 400 instrument at 400.1 MHz for ^{1}H and 100.6 MHz for ^{13}C. Chemical shifts for ^{1}H and ^{13}C are referenced to TMS via the solvent signals (^{1}H, $CHC1_3$ at 7.26 ppm; ^{13}C, $CDCl_3$ at 77.0 ppm). HRMS spectra were obtained on a Thermo Electron LTQ Orbitrap massspectrometer. Analytical chiral HPLC was performed on a Shimadzu Prominence (Chiralpak AD-H 4.6 mm i.d. × 250 mm L. column, eluted with hexane/2-PrOH 98:2, at 1.0 mL/min flow rate, column oven at 27 °C). The IR spectra were measured with the Interspec 2020 Fourier transform infrared (FTIR) spectrometer. Melting points were determined in open capillary tubes using a Büchi 535 melting-point apparatus and are uncorrected. Chiral GC analyses were performed on a Varian 3900 instrument using a permethylated β-cyclodextrin column.



Scheme 5. Preparation of epoxides **5a** and **5b**.

Preparation of (2*R*)-Dodecane-1,2-diol (12a)

A typical Sharpless asymmetric dihydroxylation protocol[16] was followed. $K_2OsO_2(OH)_4$ (7.6 mg, 0.021 mmol), 1,4,bis(9′-*O*-dihydroquinidyl) phthalazine [$(DHQD)_2PHAL$] (82 mg, 0.10 mmol), K_2CO_3 (4.1 g, 29.7 mmol), and I_2 (3.81 g, 15.0 mmol) were dissolved in a 1:1 (v/v) mixture of *t*-BuOH and H_2O (95 mL), cooled to 0 °C. Dodec-1-ene **11a** (1.77 g, 10.5 mmol) was added, and the reaction mixture was stirred at 0 °C for 6 h and then slowly warmed up to ambient temperature. The crude reaction mixture was extracted with EtOAc, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. Column chromatographic purification on silica gel with 5% MeOH in $CHCl_3$ as the eluent afforded the title product **12a** (2.06 g, 10.2 mmol, 97% yield) as white solid. R_f: 0.30 (10% MeOH in $CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$), δ: 3.71 (m, 1H, C*H*-O); 3.65 (dd, $J = 2.7$, 11.2 Hz, 1H, CH_α-O); 3.43 (dd, $J = 7.8$, 11.2 Hz, 1H, CH_β-O); 2.69 (bs, 2H, O*H*); 1.49–1.23 (m, 18H, $9 \times CH_2$); 0.88 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 72.3; 66.7; 33.1; 31.9; 29.63; 29.59; 29.58; 29.54; 29.3; 25.5; 22.7; 14.1 (CH_3). The ^1H NMR data matched the data of a commercial sample and were also consistent with previously reported data.[21]

Preparation of (2*R*)-Tetradec-13-ene-1,2-diol (12b)

$K_2OsO_2(OH)_4$ (1.8 mg, 5.0 μmol), $(DHQD)_2PHAL$ (21 mg, 25 μmol), K_2CO_3 (1.04 g, 7.5 mmol), and I_2 (0.95 g, 3.8 mmol) were dissolved in a 1:1 (v/v) mixture of *t*-BuOH and H_2O (25 mL) and cooled to 0 °C. 1,13-Tetradecadiene **11b** (0.54 g, 2.50 mmol, ca. 90% purity) was added as one portion, and the reaction mixture was stirred at 0 °C, monitored with thin-layer chromatography (TLC), and quenched with Na_2SO_3 (3.0 g) after 3.5 h when formation of tetradecane-1,2,13,14-tetrol was detected, although the substrate had not been fully consumed. Brine (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (6×15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under vacuum. Purification using column chromatography with 5% MeOH in $CHCl_3$ yielded the diol **12b** (310 mg, 1.36 mmol, 54% yield) as white solid. In addition, 240 mg of unreacted 1,13-tetradecadiene was recovered. R_f: 0.30 for the diol **12b**, and 0.10 for the by-product tetradecane-1,2,13,14-tetrol (10% MeOH in $CHCl_3$). Mp: 59–60 °C. IR (neat) $\tilde{\nu}_{max}$: 3379, 2929, 2857, 1468, 1074, 912 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 5.80 (dddd, $J = 6.7$, 6.7, 10.1, 16.9 Hz, 1H, C*H*=); 4.98 (dm, $J = 16.9$ Hz, 1H, CH_α=); 4.91 (dm,

$J = 10.1$ Hz, 1H, CH_β=); 3.67 (m, 1H, CH-OH); 3.61 (dd, $J = 2.9$, 11.2 Hz, CH_α-OH); 3.40 (dd, $J = 7.9$, 11.2 Hz, CH_β–OH); 3.23 (bs, 2H, OH); 2.02 (m, 2H, CH_2–CH=); 1.43–1.22 (m, 18H, $9 \times$ CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 139.2 (*C*H=); 114.1 (*C*H_2=); 72.3 (*C*H–O); 66.7 (*C*H_2-O); 33.8; 33.1 (*C*H_2–CH=); 29.64; 29.56 ($2 \times C H_2$); 29.54; 29.46; 29.1; 28.9; 25.6. HRMS (m/z) calcd. for $C_{14}H_{29}O_2(M + H)^+$ 229.2162; found 229.2161.

Preparation of (2*R*)-2-Hydroxydodecyl 4-Methylbenzenesulfonate (13a)

For selective tosylation of a primary hydroxyl group of a vicinal diol, a literature procedure[17] was followed.

To a solution of (2*R*)-dodecane-1,2-diol **12a** (2.00 g, 9.89 mmol), dibutyltin oxide (44 mg, 0.177 mmol), and Et_3N (1.00 g, 9.89 mmol) in CH_2Cl_2 (28 mL), *p*-toluenesulfonyl chloride (1.89 g, 9.89 mmol) was added as a solid in one portion. The reaction was stirred at ambient temperature for 18 h and then extracted with aqueous saturated $NaHCO_3$ (20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated, giving ca. 3.5 g of white amorphous solid **13a**[22] that was used without further purification for the next synthetic step. An analytical sample was obtained by chromatographic purification on silica gel (1% MeOH in $CHCl_3$). R_f: 0.50 (5% MeOH in $CHCl_3$). Mp: 59–60 °C. IR (neat) $\tilde{\nu}_{max}$: 3554, 2929, 2856, 1352, 1177, 960, 818 cm^{-1}. ^{1}H NMR (400.1 MHz, $CDCl_3$), δ: 7.80 (AA′ part of AA′BB′, 2H, CH_{Ar}); 7.36 (BB′ part of AA′BB′, 2H, CH_{Ar}); 4.04 (dd, $J = 2.5$, 9.6 Hz, 1H, CH_α-OTs); 3.88 (dd, $J = 7.1$, 9.6 Hz, 1H, CH_β-OTs); 3.83 (m, 1H, CH-OH); 2.45 (s, 3H, C_6H_4-CH_3); 1.95 (bs, 1H, OH); 1.46–1.20 (m, 18H, $9 \times$ CH_2); 0.87 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 145.0 (C_{Ar}); 132.6 (C_{Ar}); 129.9 (*C*H$_{Ar}$); 127.9 (*C*H$_{Ar}$); 74.0 (*C*H_2-OTs); 69.5 (*C*H–OH); 32.6; 31.9; 29.54; 29.50; 29.41; 29.39; 29.27; 25.2; 22.6; 21.6 (C_6H_4–*C*H_3); 14.1 (*C*H_3). Chiral HPLC analysis showed 91:9 enantiomeric ratio. HRMS (m/z) calcd. for $C_{19}H_{33}O_4S$ $(M + H)^+$ 357.2094, found 357.2091.

Preparation of (2*R*)-2-Hydroxytetradec-13-en-1-yl 4-Methylbenzenesulfonate (13b)

To a solution of (2*R*)-tetradec-13-ene-1,2-diol **12b** (200 mg, 0.88 mmol), dibutyltin oxide (4 mg, 0.016 mmol), and Et_3N (89 mg, 0.88 mmol) in CH_2Cl_2 (10 mL), *p*-toluenesulfonyl chloride (167 mg, 0.88 mmol) was added as a solid in one portion. The reaction was stirred at ambient

temperature for 4 h and then extracted with aqueous saturated $NaHCO_3$ (12 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated, giving a solid residue that was used in the next synthetic step without further purifications. Analytical sample of **13b** was obtained by chromatographic purification on silica gel (1.5% MeOH in $CHCl_3$). R_f: 0.50 (5% MeOH in $CHCl_3$). Mp: 59–60 °C. IR (neat) $\tilde{\nu}_{max}$: 3552, 2927, 2854, 1350, 1176, 958, 819 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 7.80 (AA′ part of AA′BB′, 2H, CH_{Ar}); 7.36 (BB′ part of AA′BB′, 2H, CH_{Ar}); 5.81 (dddd, $J = 6.7$, 6.7, 10.1, 16.9 Hz, 1H, CH=CH_2); 4.99 (dm, $J = 16.9$ Hz, 1H, CH=CH_α); 4.93 (dm, $J = 10.1$ Hz, Hz, 1H, CH=CH_β); 4.04 (dd, $J = 2.6$, 9.6 Hz, 1H, CH_α-OTs); 3.88 (dd, $J = 7.1$, 9.6 Hz, 1H, CH_β-OTs); 3.84 (m, 1H, CH-OH); 2.46 (s, 3H, C_6H_4–CH_3); 2.04 (m, 2H, CH_2–CH=); 1.45–1.19 (m, 18H, 9 × CH_2). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 145.0 (C_{Ar}); 139.2 (CH=CH_2); 132.7 (C_{Ar}); 129.9 (CH_{Ar}); 128.0 (CH_{Ar}); 114.1 (CH=CH_2); 74.0 (CH_2–O); 69.5 (CH–O); 33.8; 32.6; 29.52; 29.49; 29.45; 29.43; 29.41; 29.1; 28.9; 25.2; 21.7 (CH_3). HRMS (m/z) calcd. for $C_{21}H_{35}O_4S$ $(M+H)^+$ 383.2251, found 383.2247.

Preparation of (2*R*)-1,2-Epoxydodecane (5a)

K_2CO_3 (2.2 g) was added to a solution of crude **13a** (3.5 g, ca. 9.8 mmol) in a mixture of MeOH (85 mL) and CH_2Cl_2 (10 mL). After stirring at room temperature for 30 min, the solvent was evaporated under vacuum. The residue was extracted with water (3 × 15 mL), and the organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated. Purification with flash-column chromatography on silica gel (10% EtOAc in petroleum ether as eluent) gave **5a** (1.82 g, 9.88 mmol, 99% yield over two steps) as colorless oil. R_f: 0.45 ($CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$), δ: 2.90 (m, 1H, CH–O); 2.74 (dd, $J = 4.0$, 5.1 Hz, 1H, CH_α–O); 2.46 (dd, $J = 2.7$, 5.1 Hz, 1H, CH_β–O); 1.56–1.23 (m, 18H, 9 × CH_2); 0.88 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 52.4 (CH–O); 47.1 (CH_2–O); 32.5; 31.9; 29.57; 29.54; 29.4; 29.3; 26.0; 22.7; 14.1 (CH_3). The NMR data matched the data of a commercial sample and were also consistent with previously reported data.[23]

Preparation of (2*R*)-1,2-Epoxy-11-tetradecene (5b)

K_2CO_3 (200 mg, 1.45 mmol) was added to a solution of crude **13b** (330 mg, ca. 0.86 mmol) in MeOH (8 mL), stirred for 35 min,

concentrated, extracted with water, dried over Na_2SO_4, filtered, and evaporated to dryness under vacuum. Column chromatography with 10% EtOAc in petroleum ether gave 177 mg of **5b** as clear oil (0.84 mmol, 96% yield over two steps). R_f: 0.45 ($CHCl_3$). ^1H NMR (400.1 MHz, $CDCl_3$), δ: 5.81 (dddd, $J = 6.7$, 6.7, 10.1, 16.9 Hz, 1H, C*H*=CH_2); 4.98 (dm, $J = 16.9$ Hz, 1H, CH=CH_α); 4.92 (dm, $J = 10.1$ Hz, 1H, CH=CH_β); 2.89 (m, 1H, C*H*–O); 2.73 (dd, $J = 4.0$, 5.1 Hz, 1H, CH_α–O); 2.45 (dd, $J = 2.8$, 5.1 Hz, 1H, CH_β–O); 2.03 (m, 2H, CH_2–CH=); 1.55–1.24 (m, 18H, $9 \times CH_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 139.2 (*C*H=CH_2); 114.1 (CH=*C*H_2); 52.4 (*C*H–O); 47.1 (*C*H_2–O); 33.8; 32.5; 29.55; 29.53; 29.51; 29.47; 29.43; 29.1; 28.9; 26.0. HRMS (m/z) calcd. for $C_{14}H_{27}O$ $(M + H)^+$ 211.2056, found 211.2053. NMR data were in agreement with literature data for the corresponding racemic compound.[24]

Preparation of (*R*)-1-Aminododecan-2-ol (6a)

Epoxide **5a** (58 mg, 0.31 mmol) and 25% aqueous ammonium hydroxide (2 mL) was heated in EtOH (2 mL) in sealed tube at 60 °C for 16 h. Reaction mixture was concentrated under reduced pressure to afford 63 mg (>99%) of white amorphous solid, which was used without further purification. R_f: 0.52 (10:2:0.5 of $CHCl_3$/MeOH/NH_4OH). ^1H NMR (400.1 MHz, $CD_3OD/CDCl_3$), δ: 3.49 (m, 1H, CH–O); 2.67 (dd, $J = 3.2$, 13.0 Hz, 1H, CH_α–N); 2.49 (dd, $J = 8.4$, 13.0 Hz, 1H, CH_β–N); 1.46–1.19 (m, 18H, $9 \times CH_2$); 0.85 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CD_3OD/CDCl_3$), δ: 72.9 (*C*H–O); 47.7 (*C*H_2–N); 35.4; 32.4; 30.24; 30.15; 30.14 ($2 \times CH_2$); 29.9; 26.2; 23.2; 14.4 (*C*H_3). NMR data were consistent with literature data.[4a] HRMS (m/z) calcd. for $C_{12}H_{28}NO$ $(M + H)^+$ 202.2165, found 202.2163.

Preparation of N-[(2*R*)-2-Hydroxydodecyl]-4-methylbenzenesulfonamide (6b)

(2*R*)-1,2-Epoxydodecane **5a** (369 mg, 2.0 mmol), 4-methylbenzenesulfonamide (685 mg, 4.0 mmol), K_2CO_3 (28 mg, 0.20 mmol), and TEBA (46 mg, 0.20 mmol) were heated at 90 °C in 1,4-dioxane (1.0 mL) for 20 h. After cooling, the crude product was extracted with brine; the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under vacuum. Purifying the residue using column chromatography with 2.5% of MeOH in $CHCl_3$ gave **6b** (570 mg,

1.60 mmol, 80% yield) as white solid. R_f: 0.30 (5% MeOH in $CHCl_3$). Mp: 55–56 °C. IR (neat) $\tilde{\nu}_{max}$: 3508, 3291, 2928, 2857, 1331, 1163, 1095, 666, 555 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 7.75 (AA′ part of AA′BB′, 2H, CH_{Ar}); 7.30 (BB′ part of AA′BB′, 2H, CH_{Ar}); 5.23 (dd, $J = 5.2$, 7.3 Hz, 1H, N*H*); 3.68 (m, 1H, C*H*–O); 3.05 (ddd, $J = 3.0$, 7.3, 12.9 Hz, 1H, CH_α–N); 2.76 (ddd, $J = 5.2$, 8.2, 12.9 Hz, 1H, CH_β–N); 2.42 (s, 3H, C_6H_4–CH_3); 2.31 (bs, 1H, O*H*); 1.41–1.19 (m, 18H, 9 × CH_2); 0.87 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 143.5 (C_{Ar}); 136.6 (C_{Ar}); 129.7 (*C*H$_{Ar}$); 127.1 (*C*H$_{Ar}$); 70.4 (*C*H–O); 48.7 (*C*H_2–N); 34.6; 31.9; 29.55; 29.53; 29.47; 29.45; 29.3; 25.3; 22.6; 21.5 (C_6H_4–*C*H_3); 14.1 (*C*H_3). HRMS (m/z) calcd. for $C_{19}H_{34}NO_3S$ $(M + H)^+$ 356.2254, found 356.2254.

Preparation of N-[(2*R*)-2-Hydroxydodecyl]-2-nitrobenzenesulfonamide (6c)

(2*R*)-1,2-Epoxydodecane **5a** (369 mg, 2.0 mmol), 2-nitrobenzenesulfonamide (809 mg, 4.0 mmol), K_2CO_3 (28 mg, 0.20 mmol), and TEBA (46 mg, 0.20 mmol) were heated at 90 °C in 1,4-dioxane (1.0 mL) for 20 h. After cooling, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and extracted with brine; the combined organic phases were dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under vacuum. Purifying the residue using column chromatography with 2.0% of MeOH in $CHCl_3$ gave **6c** as white solid (724 mg, 1.87 mmol, 94% yield). R_f: 0.40 (5% MeOH in $CHCl_3$). Mp: 57–58 °C. IR (neat) $\tilde{\nu}_{max}$: 3540, 3350, 2930, 2857, 1545, 1367, 1168 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 8.13 (m, 1H, CH_{Ar}); 7.87 (m, 1H, CH_{Ar}); 7.74 (m, 2H, 2×*C*H_{Ar}); 5.74 (dd, $J = 5.0$, 7.1 Hz, 1H, N*H*); 3.74 (m, 1H, C*H*–O); 3.24 (ddd, $J = 3.2$, 7.1, 12.9 Hz, 1H, CH_α–N); 2.94 (ddd, $J = 5.0$, 8.0, 12.9 Hz, 1H, CH_β–N); 1.88 (bs, 1H, O*H*); 1.46–1.20 (m, 18H, 9 × CH_2); 0.88 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 148.1 (C_{Ar}); 133.60 (C_{Ar}); 133.59 (*C*H$_{Ar}$); 132.7 (*C*H$_{Ar}$); 131.1 (*C*H$_{Ar}$); 125.4 (*C*H$_{Ar}$); 70.4 (*C*H–O); 49.2 (*C*H_2–N); 34.7; 31.9; 29.56; 29.53; 29.46; 29.44; 29.3; 25.3, 22.7; 14.1 (*C*H_3). HRMS (m/z) calcd. for $C_{18}H_{31}N_2O_5S$ $(M + H)^+$ 387.1948, found 387.1948.

Preparation of (2*R*)-1-(Benzylamino)dodecan-2-ol (6d)

(2*R*)-1,2-Epoxydodecane **5a** (370 mg, 2.01 mmol) and benzylamine (655 mg, 6.11 mmol) were refluxed in 2-PrOH (1 mL) for 17 h, followed by concentration under vacuum and purification using column

chromatography on silica gel with 2.5% MeOH and 2% Et_3N in $CHCl_3$ as eluent, affording **6d** (501 mg, 1.72 mmol, 86% yield) as white solid. R_f: 0.23 (5% MeOH and 2% Et_3N in $CHCl_3$). Mp: 59–60 °C. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 7.36–7.24 (m, 5H, CH_{Ar}); 3.83 (d, $J = 13.3$ Hz, CH_α–Ph); 3.77 (d, $J = 13.3$ Hz, CH_β–Ph); 3.61 (m, 1H, C*H*–O); 2.76 (dd, $J = 3.1$, 12.1 Hz, 1H, CH–CH_α–N); 2.46 (dd, $J = 9.4$, 12.1 Hz, 1H, CH–CH_β–N); 1.49–1.16 (m, 18H, $9 \times CH_2$). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 140.1 (C_{ipso}); 128.4 (CH_{Ar}); 128.0 (CH_{Ar}); 127.1 (CH_{para}); 69.6 (*C*H–O); 54.8 (CH_2); 53.6 (CH_2); 35.0; 31.9; 29.7; 29.60; 29.57; 29.3; 25.7; 22.7; 14.1 (CH_3). ^1H NMR data were in an agreement with the corresponding racemic compound.[27] HRMS (m/z) calcd. for $C_{19}H_{34}NO$ $(M+H)^+$ 292.2635, found 292.2635.

Preparation of (2*R*)-1-[(2-Aminoethyl)amino]dodecan-2-ol (7a)

The solution of epoxide **5a** (105 mg, 0.568 mmol), ethylene-1,2-diamine (196 mg, 3.25 mmol) in 10 mL of EtOH was stirred at 50 °C for 4 h until TLC indicated complete consumption of the starting materials. The reaction mixture was extracted with CH_2Cl_2 and brine (solid NaOH was added to brine for better phase separation). The combined organic phases were filtered and dried, and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel (10:2:0.5 of $CHCl_3$/MeOH/NH_4OH) to attain the desired aminated product **7a** (137 mg, 0.562 mmol, 99% yield) as colorless oil. R_f: 0.29 (10:2:0.5 of $CHCl_3$/MeOH/NH_4OH). IR (neat) $\tilde{\nu}_{max}$: 3291, 2927, 2856, 1666, 1469, 1099 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 3.60 (m, 1H, C*H*–O); 2.82 (m, 2H, CH_2–NH_2); 2.71 (m, 1H, CH–CH_α–N); 2.67 (m, 2H, NH–CH_2); 2.45 (dd, $J = 9.2$, 12.2 Hz, 1H, CH–CH_β–N); 2.01 (bs, 3H, N*H* + O*H*); 1.47–1.20 (m, 18H, $9 \times CH_2$); 0.87 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 69.6 (*C*H–O); 55.3; 52.1; 41.7; 35.1; 31.9; 29.7; 29.57; 29.56; 29.3; 25.7; 22.6; 14.1 (CH_3). HRMS (m/z) calcd. for $C_{14}H_{33}N_2O$ $(M+H)^+$ 245.2587, found 245.2587.

Preparation of (2*R*)-1-{Benzyl[2-(benzylamino)ethyl]amino}dodecan-2-ol (7b)

(2*R*)-1,2-Epoxydodecane **5a** (398 mg, 2.16 mmol) and *N*,*N*′-dibenzylethylene-1,2-diamine (1.5 mL, ca. 6.4 mmol) were refluxed in 2-PrOH (1.5 mL) for 4 h. After cooling, the solvent was evaporated under vacuum, and the residue was purified with flash chromatography (1%

MeOH in $CHCl_3$), giving **7b** as slightly yellowish oil (737 mg, 1.74 mmol, 81% yield). R_f: 0.5 (10% MeOH in $CHCl_3$). IR (neat) $\tilde{\nu}_{max}$: 3320, 2928, 2856, 1455, 740, 700 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 7.34–7.21 (m, 10H, CH_{Ar}); 3.80 (d, $J = 13.5$ Hz, 1H, CH_α–Ph); 3.70 (s, 2H, CH_2–Ph); 3.50 (d, $J = 13.5$ Hz, 1H, CH_β–Ph); 3.65 (m, 1H, C*H*–O); 2.74 (m, 2H); 2.64 (m, 1H); 2.55 (m, 1H); 2.51 (dd, $J = 3.0$, 13.0 Hz, 1H, CH–CH_α–N); 2.41 (dd, $J = 9.9$, 13.0 Hz, 1H, CH–CH_β–N); 1.49–1.17 (m, 18H, $9 \times CH_2$); 0.89 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 140.1 (C_{Ar}); 139.1 (C_{Ar}); 129.0; 128.34; 128.32; 128.0; 127.1; 126.9; 68.3; 60.7; 60.0; 53.5; 46.7; 34.8; 31.9; 29.8; 29.59; 29.58; 29.3; 25.8; 22.7; 14.1 (CH_3). HRMS (m/z) calcd. for $C_{28}H_{45}N_2O$ $(M + H)^+$ 425.3526, found 425.3512.

Preparation of (2*R*)-2-*tert*-Butyldimethylsilyloxy-1-iodododecane (9)

Imidazole (477 mg, 7.0 mmol) and TBDMSCl (423 mg, 2.8 mmol) were added to a solution of tosylate **13a** (1.0 g, 2.8 mmol) in DMF (3.0 mL). After stirring at room temperature for 6 h, the reaction mixture was diluted with brine and extracted with EtOAc (3×15 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated. Purification by flash chromatography (gradual elution 0–5% EtOAc/hexanes) afforded 1.28 g (97%) of colorless oil as (2*R*)-2-*tert*-butyldimethylsilyloxy-1-(4-methyl-benzenesulfonyloxy)dodecane. Part of this silyl-protected tosylate (910 mg, 2.23 mmol) was dissolved in acetone (5 mL). NaI (1.67 g, 11.15 mmol) was added, and the reaction mixture was refluxed for 20 h. After cooling down, the reaction mixture was diluted with brine, extracted with EtOAc (3×20 mL), dried over anhydrous Na_2SO_4, and concentrated to give 812 mg (85%) of compound **9** as slightly yellowish oil. R_f: 0.70 ($CHCl_3$). IR (neat) $\tilde{\nu}_{max}$: 2932, 2859, 1473, 1257, 1076 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 3.54 (ddt, $J = 5.1$, 6.5, 11.6 Hz, 1H, C*H*–O); 3.19 (d, $J = 5.1$ Hz, 2H, CH_2–I); 1.64–1.21 (m, 18H, $9 \times CH_2$); 0.90 [s, 9H, $C(CH_3]_3$); 0.88 (vt, 3H, CH_2–CH_3); 0.08 (d, $J = 11.6$ Hz, 6H, Si–CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 71.4; 36.9; 31.9; 29.59; 29.56; 29.54; 29.53; 29.3; 25.8; 24.9; 22.7; 18.1; 14.2; 14.1; −4.4; −4.6. HRMS (m/z) calcd. for $C_{18}H_{40}IOSi$ $(M + H)^+$ 427.1888, found $(M + H)^+$ 427.1877.

Preparation of 1-[(2-Aminoethyl)amino]propan-2-ol (10)

Propylene oxide (348 μL, 5.0 mmol), ethylene-1,2-diamine (1.0 mL, 14.9 mmol), and MeCN (0.6 mL) were heated in a sealed tube at 65 °C

for 24 h. After cooling down, the reaction mixture was concentrated to afford 718 mg of crude product **10** (estimated yield 68%) as slightly yellowish oil. The crude product contains unreacted ethylene-1,2-diamine. ^{1}H NMR (400.1 MHz, $CDCl_3$), δ: 3.77 (ddq, $J = 3.1$, 6.3, 9.2 Hz, 1H, C*H*–O); 2.74 (m, 2H); 2.64 (m, 2H); 2.59 (dd, $J = 3.1$, 12.2 Hz, 1H, CH–CH_α-N); 2.42 (dd, $J = 9.2$, 12.2 Hz, 1H, CH–CH_β–N); 1.10 (d, $J = 6.3$ Hz, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 65.6 (*C*H–O); 56.5; 51.2; 40.8; 20.6 (*C*H_3). ^{1}H NMR and ^{13}C NMR spectra were consistent with literature data.[25] HRMS (m/z) calcd. for $C_5H_{15}N_2O$ $(M + H)^+$ 119.1179, found 119.1177.

Preparation of *N*,*N*′-Bis(2-hydroxypropyl)ethylene-1,2-diamine (11)

Propylene oxide (1.0 mL, 14.2 mmol) and MeCN (0.6 mL) were added to amino alcohol **10** (718 mg, ca. 1:1 mixture of **10** and ethylene-1,2-diamine based on ^{13}C NMR). The reaction mixture was heated at in at 65 °C for 24 h in a sealed tube. After cooling down, the reaction mixture was concentrated to give 993 mg of **11** as an amorphous sticky solid (estimated yield 87%). The crude product contains unreacted ethylene-1,2-diamine.^{1}H NMR (400.1 MHz, $CDCl_3$), δ: 3.78 (ddq, $J = 3.1$, 6.3, 9.2 Hz, 2H, C*H*–O); 2.82 (m, 4H, N–CH_2–CH_2–N); 2.72 (dd, $J = 3.1$, 12.2 Hz, 2H, CH–CH_α–N); 2.42 (dd, $J = 9.2$, 12.2 Hz, 2H, CH–CH_β–N); 1.15 (d, $J = 6.3$ Hz, 6H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 65.6 (*C*H–O); 56.7; 52.0; 41.8; 20.4 (*C*H_3). ^{1}H NMR spectral data are consistent with literature data.[26] HRMS (m/z) calcd. for $C_8H_{21}N_2O_2$ $(M + H)^+$ 177.1598, found 177.1599.

Preparation of *N*-[(2*R*)-2-Hydroxytetradec-13-en-1-yl]-*N*-[(2*R*)-2-hydroxydodecyl]-4-methylbenzenesulfonamide (3b)

N-[(2*R*)-2-Hydroxydodecyl]-4-methylbenzenesulfonamide **6b** (345 mg, 0.97 mmol), (2*R*)-1,2-epoxy-11-tetradecene **5b** (170 mg, 0.81 mmol), K_2CO_3 (13 mg, 94 μmol), and TEBA (19 mg, 83 μmol) were heated at 90 °C in 1,4-dioxane (1.0 mL) for 1 week. After cooling, it was extracted with brine and $CHCl_3$, dried over anhydrous Na_2SO_4, filtered, and evaporated. Purification by column chromatography using 0.5–3.0% MeOH gradient in $CHCl_3$ afforded unreacted epoxide **5b** (50 mg), unreacted tosylamide **6b**, desired products **3b** as diastereoisomers (combined yield 53%, 241 mg, 0.43 mmol), and a sideproduct coming from the Hofmann decomposition of TEBA. Spectral data

given only for the major diastereoisomer of the product. R_f: 0.46 (5% MeOH in $CHCl_3$). Mp: 65–66.5 °C. IR (neat), $\tilde{\nu}_{max}$: 3312, 2923, 2853, 1347, 1157 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 7.68 (AA′ part of AA′BB′, 2H, CH_{Ar}); 7.31 (BB′ part of AA′BB′, 2H, CH_{Ar}); 5.80 (dddd, $J = 6.7$, 6.7, 10.2, 17.0 Hz, 1H, CH=); 4.98 (dddd, $J = 1.6$, 1.6, 2.2, 17.0 Hz, 1H, CH_α=); 4.91 (dddd, $J = 1.2$, 1.2, 2.2, 10.2 Hz, 1H, CH_β=); 3.90 (m, 2H, CH–O); 3.46 (bs, 2H, OH); 3.01 (m, 4H, $2 \times$ CH_2–N); 2.42 (s, 3H, C_6H_4–CH_3); 2.02 (m, 2H, CH_2–CH=); 1.47–1.20 (m, 36H, $18 \times$ CH_2); 0.87 (vt, 3H, CH_2–CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 143.5 (C_{Ar}); 139.1 (CH=); 135.1 (C_{Ar}); 129.7 (CH$_{Ar}$); 127.4 (CH$_{Ar}$); 114 (CH_2=); 70.1 (CH–O); 56.5 (CH$_2$–N); 34.6; 33.7 (CH$_2$–CH=); 31.8; 29.61; 29.60; 29.56; 29.55; 29.53; 29.52; 29.51; 29.4; 29.3; 29.1; 28.9; 25.5; 22.6; 21.4 (C_6H_4–CH$_3$); 14.1 (CH_2–CH$_3$). HRMS (m/z) calcd. for $C_{33}H_{60}NO_4S$ $(M + H)^+$ 566.4238, found 566.4242.

Preparation of *N*-[(2*R*)-2-Hydroxytetradec-13-en-1-yl]-*N*-[(2*R*)-2-hydroxydodecyl]-2-nitrobenzenesulfonamide (3c)

N-[(2*R*)-2-Hydroxydodecyl]-2-nitrobenzenesulfonamide **6c** (606 mg, 1.57 mmol), (2*R*)-1,2-epoxy-11-tetradecene **5b** (300 mg, 1.43 mmol), K_2CO_3 (22 mg, 0.16 mmol), and TEBA (36 mg, 0.16 mmol) were heated at 90 °C in 1,4-dioxane (2.0 mL) for 10 days. After cooling, the crude reaction mixture was diluted with brine, extracted with CH_2Cl_2, dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness under vacuum. Purification by column chromatography with 1.3% MeOH in $CHCl_3$ as eluent afforded the unreacted **5b** and **6c**, together with the desired product **3c** as two diastereoisomers (460 mg, 0.77 mmol, combined yield of the two diastereoisomers 54%). In addition, a similar side product, coming from the decomposition of TEBA, was observed. Spectral data given only for the major diastereoisomer of the product. R_f: 0.52 (5% MeOH in $CHCl_3$). Mp: 42–43.5 °C. IR (neat) $\tilde{\nu}_{max}$: 3366, 2932, 2858, 1551, 1469, 1375, 1167, 583 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 8.00 (m, 1H, CH_{Ar}); 7.70 (m, 2H, CH_{Ar}); 7.61 (m, 1H, CH_{Ar}); 5.80 (dddd, $J = 6.7$, 6.7, 10.1, 16.9 Hz, 1H, CH=CH_2); 4.98 (dm, $J = 16.9$ Hz, 1H, CH_α=); 4.91 (dm, $J = 10.1$ Hz, 1H, CH_β=); 3.89 (m, 2H, CH-O); 3.26 (m, 6H, CH_2–N–CH_2 + $2 \times$ OH); 2.03 (m, 2H, CH_2–CH=); 1.46–1.19 (m, 36H, $18 \times$ CH_2); 0.87 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 148.4 (C_{Ar}); 139.2 (CH=); 133.7 (CH$_{Ar}$); 132.0 (C_{Ar}); 131.6 (CH$_{Ar}$); 130.9 (CH$_{Ar}$); 124.1 (CH$_{Ar}$); 114.0 (CH_2=); 69.6 (CH–O); 55.6 (CH$_2$–N); 34.6; 33.8 (CH$_2$–CH=); 31.9; 29.57; 29.56 ($2 \times C$H$_2$); 29.54; 29.53;

29.51; 29.50; 29.48; 29.44; 29.3; 29.1; 28.9; 25.4; 22.6; 14.1 (CH_3). HRMS (m/z) calcd. for $C_{32}H_{57}N_2O_6S$ $(M+H)^+$ 597.3932, found 597.3935.

Preparation of (2*R*)-1-[Benzyl((2R)-2-hydroxydodecyl)amino]tetradec-13-en-2-ol (3d)

(2*R*)-1-(Benzylamino)dodecan-2-ol **6d** (207 mg, 0.71 mmol) and (2*R*)-2-(dodec-11-en-1-yl)oxirane **5b** (150 mg, 0.71 mmol) were refluxed in 2-PrOH (5 mL) for 20 h. Purification using column chromatography with 1% MeOH in $CHCl_3$ gave **3d** (309.5 mg, 0.617 mmol, 87% yield) as colorless oil. R_f: 0.20 (20% EtOAc in hexanes). IR (neat), $\tilde{\nu}_{max}$: 3411, 2931, 2858, 1458, 1080, 911, 743, 701 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 7.36–7.24 (m, 5H, CHAr); 5.81 (dddd, $J = 6.7$, 6.7, 10.1, 16.9 Hz, 1H, C*H*=CH_2); 4.99 (dm, $J = 16.9$ Hz, 1H, CH=CH_α); 4.93 (dm, $J = 10.1$ Hz, 1H, CH=CH_β); 3.88 (d, $J = 13.5$ Hz, 1H, CH_α-Ph); 3.66 (m, 2H, 2 × C*H*–O); 3.47 (d, $J = 13.5$ Hz, 1H, CH_β–Ph); 2.74 (bs, O*H*); 2.45 (m, 4H, CH_2–N–CH_2); 2.03 (m, 2H, CH_2–CH=); 1.45–1.18 (m, 36H, 18 × CH_2); 0.88 (vt, 3H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 139.3 (*C*H=CH_2); 138.4 (C_{ipso}); 129.0 (*C*H_{Ar}); 128.5 (*C*H_{Ar}); 127.4 (*C*H_{para}); 114.1 (CH=*C*H_2); 67.9 (*C*H–O); 60.6 (CH–*C*H_2–N); 59.7 (*C*H_2–Ph); 34.9; 33.8 (*C*H_2–CH=); 31.9; 29.7; 29.59; 29.56; 29.55; 29.47; 29.3; 29.1; 28.9; 25.7; 22.7; 14.1 (*C*H_3). HRMS (m/z) calcd. for $C_{33}H_{60}NO_2$ $(M+H)^+$ 502.4619, found 502.4601.

Preparation of *N,N′*-Bis[(2R)-2-hydroxydodecyl]-*N,N′*-dibenzylethylene-1,2-diamine (4b)

(2*R*)-1,2-Epoxydodecane **5a** (50 mg, 0.27 mmol) and *N,N′*-dibenzylethylene-1,2-diamine (33 μL, 0.14 mmol) were refluxed in 2-PrOH (0.5 mL) for 24 h. Purification with a flash column using 1% MeOH in $CHCl_3$ as eluent gave the product **4b** as oil (61 mg, 0.10 mmol, 74% yield). R_f: 0.75 (10% MeOH in $CHCl_3$). IR (neat) $\tilde{\nu}_{max}$: 3429, 2928, 2857, 1458, 1078 cm^{-1}. ^1H NMR (400.1 MHz, $CDCl_3$), δ: 7.31–7.16 (m, 10H, CH_{Ar}); 4.55 (bs, 2H, O*H*); 3.73 (d, $J = 13.2$ Hz, 2H, CH_α–Ph); 3.67 (m, 2H, C*H*–O); 3.26 (d, $J = 13.2$ Hz, 2H, CH_β–Ph); 2.83 (m, 2H, N–CH_α–CH_α–N); 2.37 (m, 4H, CH–CH_2–N); 2.27 (m, 2H, N–CH_β–CH_β–N); 1.49–1.17 (m, 36H, 18 × CH_2); 0.89 (vt, 6H, CH_3). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 138.1 (C_{ipso}); 129.2 (*C*H_{Ar}); 128.3 (*C*H_{Ar}); 127.1 (*C*H_{para}); 67.3 (*C*H–O); 60.6 (CH–*C*H_2–N); 59.2 (*C*H_2–Ph); 50.8 (N–*C*H_2–*C*H_2–N); 34.8; 31.9; 29.8; 29.60; 29.58; 29.3; 25.7; 22.7; 14.1 (*C*H_3). HRMS (m/z) calcd. for $C_{40}H_{69}N_2O_2$ $(M+H)^+$ 609.5354, found 609.5355.

Preparation of *N,N′*-Bis[(2*R*)-2-hydroxydodecyl]ethylene-1,2-diamine (4a)

Dibenzyl derivative **4b** (51 mg, 0.083 mmol) and 10% palladium on carbon (17 mg) was shaken in MeOH (5 mL) under the atmosphere of H_2 gas (1 bar) overnight. Filtration and evaporation under vacuum afforded **4a** as white powder (29 mg, 82%). R_f: 0.1 (10% MeOH in $CHCl_3$). Mp: 142–144 °C. IR (neat), $\tilde{\nu}_{max}$: 3374, 2925, 2855, 1471, 1137 cm^{-1}. ^1H NMR (400.1 MHz, $CD_3OD/CDCl_3$), δ: 3.72 (m, 2H, 2 × C*H*–O); 2.98 (m, 4H, N–CH_2–CH_2–N); 2.85 (dd, $J = 2.9$, 12.3 Hz, 2H, CH–CH_α–N); 2.66 (dd, $J = 9.1$, 12.3 Hz, 2H, CH–CH_β–N); 1.48–1.21 (m, 36H, 18 × CH_2); 0.86 (vt, 6H, CH_3). ^{13}C NMR (100.6 MHz, $CD_3OD/CDCl_3$), δ: 69.3 (*C*H–O); 54.6 (CH–*C*H_2–N); 46.6 (N–*C*H_2–*C*H_2–N); 35.8; 32.5; 30.27; 30.23; 30.21; 29.9; 26.1; 23.2; 14.3 (*C*H_3). HRMS (m/z) calcd. for $C_{26}H_{57}N_2O_2$ $(M + H)^+$ 429.4415, found 429.4417.

ACKNOWLEDGMENTS

This work was supported by the Grants Nos. 6520, 7009, 7260, and 7517 from the Estonian Science Foundation, and Estonian Targeted Financing Grant TLOTI0073. We are grateful to Prof. Peter Somfai for fruitful discussions and critically reading the manuscript. We thank Lauri Peil for HRMS analysis. We thank the Estonian State Agency of Medicines Quality Control Laboratory for giving access to FTIR and melting-point determination apparatuses.

REFERENCES

1. Ager, D. J.; Prakash, I.; Schaad, D. R. 1,2-Amino alcohols and their heterocyclic derivatives as chiral auxiliaries in asymmetric synthesis. *Chem. Rev.* **1996**, *96*, 835–876.
2. Winsor, P. A. Binary and multicomponent solutions of amphiphilic compounds: Solubilization and the formation, structure, and theoretical significance of liquid crystalline solutions. *Chem. Rev.* **1968**, *68*, 1–40.
3. (a) Hepworth, P. Non-ionic surfactants. In *Chemistry and Technology of Surfactants*; R. Farm (Ed.); Blackwell Publishing Ltd: Oxford, UK, 2006; chapter 5; (b) Holmberg, K.; Jonsson, B.; Kronberg, B.; Lindman, B. *Surfactants and Polymers in Aqueous Solution*, 2nd ed.; Wiley & Sons: Chichester, England, 2003; pp. 1–37.
4. (a) Taveira, A. F.; Hyaric, M. L.; Reis, E. F. C.; Araujo, D. P.; Ferreira, A. P.; de Souza, M. A.; Alves, L. L.; Lourenco, M. C. S.; Vicente, F. R. C.; de Almeida, M. V. Preparation and antitubercular activities of alkylated amino alcohols and their glycosylated derivatives. *Bioorg. Med. Chem.*

2007, *15*, 7789–7794; (b) Tewari, N.; Tiwari, V. K.; Tripathi, R. P.; Chaturvedi, V.; Srivastava, A.; Srivastava, R.; Shukla, P. K.; Chaturvedi, A. K.; Gaikwad, A.; Sinha, S.; Srivastava, B. S. Synthesis of galactopyranosyl amino alcohols as a new class of antitubercular and antifungal agents. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 329–332.

5. Spichiger-Keller, U. E. Ionophores, ligands, and reactands. *Anal. Chim. Acta* **1999**, *400*, 65–72.
6. World Health Organization. *Treatment of Tuberculosis: Guidelines for National Programmes*; 2003. Available at http://whqlibdoc.who.int/hq/2003/WHO_CDS_TB_2003.313_eng.pdf.
7. Yendapally, R.; Lee, R. E. Design, synthesis, and evaluation of novel ethambutol analogues. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 1607–1611.
8. Tripathi, R. P.; Tripathi, R.; Tiwari, V. K.; Bala, L.; Sinha, S.; Srivastava, A.; Srivastava, R.; Srivastava, B. S. Synthesis of glycosylated β-amino acids as new class of antitubercular agents. *Eur. J. Med. Chem.* **2002**, *37*, 773.
9. Tewari, N.; Tiwari, V. K.; Tripathi, R. P.; Chaturvedi, V.; Srivastava, A.; Srivastava, R.; Shukla, P. K.; Chaturvedi, A. K.; Gaikwad, A.; Sinha, S.; Srivastava, B. S. Synthesis of galactopyranosyl amino alcohols as a new class of antitubercular and antifungal agents. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 329–332.
10. de Almeida, M. V.; Le Hyaric, M.; Amarante, G. W.; Silva Lourenco, M. C.; Lima Brandao, M. L. Synthesis of amphiphilic galactopyranosyl diamines and amino alcohols as antitubercular agents. *Eur. J. Med. Chem.* **2007**, *42*, 1076–1083, and references therein.
11. Bermejo, A.; Figadère, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. Acetogenins from Annonaceae: Recent progress in isolation, synthesis, and mechanisms of action. *Nat. Prod. Rep.* **2005**, *22*, 269–303.
12. (a) Wang, M.; Shen, J. Synthesis of simplified analogue of acetogenin bearing *N,N′*-dibenzyl ethylenediamine moiety. *Chin. J. Synth. Chem.* **2006**, *14*, 337–341; (b) Wang, M.; Chen, Y.; Lou, L.; Tang, W.; Wang, X.; Shen, J. Synthesis of pyrrolidine analogues of solamin. *Tetrahedron Lett.* **2005**, *46*, 5309–5312.
13. (a) Larrow, J. F.; Schaus, S. E.; Jacobsen, E. N. Kinetic resolution of terminal epoxides via highly regioselective and enantioselective ring opening with $TMSN_3$: An efficient, catalytic route to 1,2-amino alcohols. *J. Am. Chem. Soc.* **1996**, *118*, 7420–7421; (b) Olofsson, B.; Khamrai, U.; Somfai, P. A regio- and stereodivergent synthesis of vic-amino alcohols. *Org. Lett.* **2000**, *2*, 4087–4089; (c) Sekar, G.; Singh, V. K. An efficient method for cleavage of epoxides with aromatic amines. *J. Org. Chem.* **1999**, *64*, 287–289.
14. (a) Adolfsson, H.; Balan, D. Metal-catalyzed synthesis of epoxides; In *Aziridines and Epoxides in Organic Synthesis*; A. Yudin (Ed.); Wiley-VCH: Weinheim, Germany, 2006; pp. 185–228; (b) Jacobsen, E. N. Asymmetric catalytic epoxidation of unfunctionalized olefins; In *Catalytic Asymmetric Synthesis*; I. Ojima (Ed.); VCH: New York, 1993; pp. 159–202; (c) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic asymmetric dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483–2547.

15. (a) See Möller, F. *Methoden der Organische Chemie (Houben-Weyl),* 4th ed.; E. Müller (Ed.); Thieme Verlag: Stuttgart, 1957; vol. 11/1, pp. 311–326; (b) Mousseron, M.; Jullien, J.; Jolchine, Y. Alicyclic series, XXXIV: Preparation and properties of substituted amines. *Bull. Soc. Chim. Fr.* **1952**, 757–766; (c) Chini, M.; Crotti, P.; Macchia, F. Regioalternating selectivity in the metal salt catalyzed aminolysis of styrene oxide. *J. Org. Chem.* **1991**, *56*, 5939–5942; (d) Caron, M.; Sharpless, K. B. Titanium isopropoxide–mediated nucleophilic openings of 2,3-epoxy alcohols: A mild procedure for regioselective ring-opening. *J. Org. Chem.* **1985**, *50*, 1557–1560.
16. Crispino, G. A.; Jeong, K. S.; Kolb, H. C.; Wang, Z. M.; Xu, D.; Sharpless, K. B. Improved enantioselectivity in asymmetric dihydroxylations of terminal olefins using pyrimidine ligands. *J. Org. Chem.* **1993**, *58*, 3785–3786.
17. Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. Dibutyltin oxide catalyzed selective sulfonylation of α-chelatable primary alcohols. *Org. Lett.* **1999**, *1*, 447–450.
18. Foglia, T. A.; Swern, D. Pseudo-halogens. VII. New synthesis of aziridines and oxazolidones. *J. Org. Chem.* **1967**, *32*, 75–78.
19. Lupi, V.; Albanese, D.; Landini, D.; Scaletti, D.; Penso, M. Synthesis of 2,6-disubstituted morpholines through regioselective oxiranes ring opening by tosylamide under PTC conditions. *Tetrahedron* **2004**, *60*, 11709–11718.
20. (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. 2- and 4-Nitrobenzenesulfonamides: Exceptionally versatile means for preparation of secondary amines and protection of amines. *Tetrahedron Lett.* **1995**, *36*, 6373–6374; (b) Kan, T.; Fukuyama, T. Ns strategies: A highly versatile synthetic method for amines. *Chem. Comm.* **2004**, 353–359.
21. Zeng, B.-B.; Wu, Y.; Jiang, S.; Yu, Q.; Yao, Z.-J.; Liu, Z.-H.; Li, H.-Y.; Li, Y.; Chen, X.-G.; Wu, Y.-L. Studies on mimicry of naturally occurring annonaceous acetogenins: Non-THF analogues leading to remarkable selective cytotoxicity against human tumor cells. *Chem. Eur. J.* **2003**, *9*, 282–290.
22. Chen, C. S.; Liu, Y. C. A chemoenzymatic access to optically active 1,2-epoxides. *Tetrahedron Lett.* **1989**, *30*, 7165–7168.
23. Altinis Kiraz, C. I.; Mora, L.; Jimenez, L. S. Oxidation of alkenes by oxodiperoxomolybdenum: Trialkyl(aryl)phosphine oxide complexes. *Synthesis* **2007**, 92–96.
24. Hamamoto, M.; Nakayama, K.; Nishiyama, Y.; Ishii, Y. Oxidation of organic substrates by a molecular oxygen/aldehyde/heteropolyoxometalate system. *J. Org. Chem.* **1993**, *58*, 6421–6425.
25. SciFinder Scholar: ^{13}C NMR, Spectrum ID CNCC-74760-160M. Spectral data were obtained from Wiley Subscripton Services, Inc. (US).
26. Smith, D. J.; Patel, S. R. Acrylate and methacrylate monomers and hydrogel polymers. Eur. Pat. Appl. 0263605, September 15, 1987.
27. Bolton, G. L.; Padia, J. K.; Trivedi, B. K. Phosphorus containing compounds as antihypercholesterolemic and antiatherosclerotic agents. U.S. Patent 5,208,224, May 4, 1993.