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Asymmetric Synthesis of Dialkyloxy-3-alkylammonium Cationic Lipids

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Abstract: The cationic diether-linked cytofectin DOTMA (available commercially as a mixture, Lipofectin comprised of DOTMA:DOPE, 1:1) and analogues including DIMRIE and DORIE are frequently used for in vitro and in vivo transfections. Despite this wide usage direct synthetic routes to the optical isomers have received little attention to date. Here we describe strategies to synthesize enantiomers of DOTMA and analogues, including an extremely concise procedure to the trimethylammonium salts. One strategy utilized *N*-protection, as the imine, with concomitant ether formation and deprotection during the workup. Methylation of the 1-amino-2,3-dialkyloxypropane then generated the trimethylammonium cationic lipids directly. This methodology was extended to synthesize a novel headgroup functionalized lipid. A second route was also developed using an alternative chiral synthon.

The use of synthetic cationic lipids in binding polynucleotides and facilitating gene transfer continues to develop as an alternative to viral-mediated gene delivery. Since the initial work by Felgner and co-workers on the synthesis of DOTMA **1**,[1] the range of synthetic lipids reported for use as gene delivery vectors has expanded significantly. Several reagents have become commercially available, for example, Lipofectin, a coformulation of DOTMA **1** with naturally available neutral lipid DOPE **2** (Figure 1).[2,3] DOTMA contains a glycerol backbone with two oleyl chains and a trimethylammonium cationic headgroup. Related diether-linked analogues include DIMRIE **3** and DORIE **4**, possessing C14:0 and C18:1 chain lengths, respectively, and *N*,*N*-dimethyl-*N*-ethanolamine headgroups.[4] Several diester-linked amphiphiles have also been reported including DOTAP **5**, which was designed to be more readily metabolized,[5] and DORI **6**.[6] Interestingly, although naturally available DOPE is available in optically active form (*R*-isomer) most diester- and diether-linked glycerol-based lipids are synthesized and used as a racemic mixture, having been prepared from racemic 3-(dimethylamino)-1,2-propanediol. Exceptions include synthesis of the more synthetically accessible diesters, for example, (*R*)-DORI,[6] which was prepared from commercially available optically active glycidol in 5 steps, and the diester pcTG201 **7**, also synthesized from glycidol.[7] Furthermore, in his original patent Felgner described the synthesis of the diether (*S*)-DOTMA in 5 steps from D-mannitol-3,4-acetonide; however, this route from the chiral pool would not readily afford the (*R*)-isomer.[8]

The LID vector, a synthetic gene delivery system comprised of Lipofectin (L), an integrin-targeting peptide (I), and DNA has previously been shown to have high transfection efficiency in vitro and in vivo.[9,10] In the course of our studies investigating the structural features of DOTMA which have a key bearing on the transfection properties of the LID ternary vector[9,10] a concise, flexible synthesis of both enantiomers of the diether-linked dialkyloxy-3-alkylammonium cationic lipids was required. Herein we describe the first synthetic route to both (*R*)- and (*S*)-1,2-dialkyloxy-3-trimethylammonium salts and alternative strategies to access dimethylammonium cationic lipids with a stereospecific center at C-2.

The synthesis of stereochemically defined diester-linked cationic lipids has been carried out with (*R*)-glycidol via ring opening and amine formation then attachment of acyl moieties incorporating protecting groups where necessary.[6,7] Our aim was to initially develop a concise synthetic route to both enantiomers of the diether trimethylammonium cytofectins such as DOTMA, suitable for analogue preparation, and therefore we considered using 3-amino-1,2-propanediol **8**, which is commercially available as both isomers, as our starting material. We envisaged that *N*-protection, diether formation, and then quaternization would directly generate the cationic lipids. Several *N*-protecting groups were considered, with a view to removal in the presence of alkene moieties. Initially, *N*-Boc protection was carried out[11] to give *N*-Boc-3-amino-1,2-propandiol, which has also been prepared from (*R*)-glycidol to access the diester lipid series.[7] However, subsequent reaction with NaH and oleyl mesylate[12] led to neighboring alkoxide attack and *N*-alkylation. Similar intramolecular reactions at the *N*-Boc carbonyl group have been reported during the synthesis of polymer-supported oxazolidin-2-ones[13] and in the synthesis of oxazolidinones with *N*-Boc-*β*-amino

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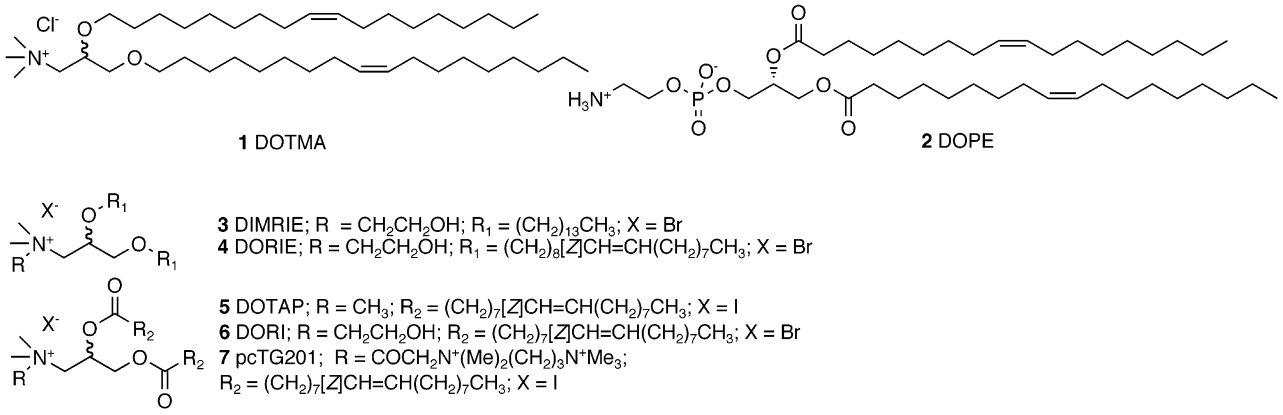
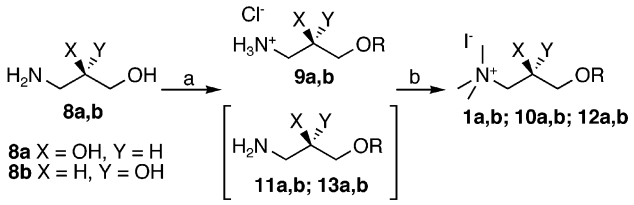


FIGURE 1. Lipids used in gene delivery.

SCHEME 1. Formation of 1,2-Dialkyloxy-3-trimethylammonium Salts[a]



9a (2*R*); X = OR, Y = H; R = $(CH_2)_{13}CH_3$
9b (2*S*); X = H, Y = OR; R = $(CH_2)_{13}CH_3$
10a (2*R*); X= OR, Y = H; R = $(CH_2)_{13}CH_3$
10b (2*S*); X = H, Y = OR; R = $(CH_2)_{13}CH_3$
11a (2*R*); X = OR, Y = H; R = $(CH_2)_{10}$[*Z*]CH=CHCH_2CH_3
11b (2*S*); X = H, Y = OR; R = $(CH_2)_{10}$[*Z*]CH=CHCH_2CH_3
12a (2*R*); X= OR, Y = H; R = $(CH_2)_{10}$[*Z*]CH=CHCH_2CH_3
12b (2*S*); X = H, Y = OR; R = $(CH_2)_{10}$[*Z*]CH=CHCH_2CH_3
13a (2*R*); X= OR, Y = H; R = $(CH_2)_8$[*Z*]CH=CH$(CH_2)_7CH_3$
13b (2*S*); X = H, Y = OR; R = $(CH_2)_8$[*Z*]CH=CH$(CH_2)_7CH_3$
1a (2*R*)-DOTMA; X = OR, Y = H; R = $(CH_2)_8$[*Z*]CH=CH$(CH_2)_7CH_3$
1b (2*S*)-DOTMA; X = H, Y = OR; R = $(CH_2)_8$[*Z*]CH=CH$(CH_2)_7CH_3$

[a] Reagents and conditions: (a) (i) PhCHO, Na_2SO_4, CH_2Cl_2, 18 h, (ii) NaH, THF, MsOR, reflux, 72 h, (iii) 1 M HCl/EtOH (1:1), 6 h; (b) MeI, NaOH, 90 °C, 18 h.

alcohols.[14] Interestingly, Kokotos has reported the *O*-alkylation of *N*-Boc-3-amino-1,2-propanediol using saturated alkyl halides and a biphasic solvent mixture containing sodium hydroxide for the synthesis of inhibitors of digestive lipases, but did not report the formation of any oxazolidinone side products.[11] Our previous studies investigating such diether synthesis had established that for unsaturated alkyl chains, activation as the mesylate led to consistently higher yields. Therefore, since mesylates are not compatible with aqueous basic conditions, an alternative protecting group was used.

Accordingly, imine *N*-protection[15] was investigated as shown in Scheme 1. Protection of (2*R*)-3-amino-1,2-propanediol **8a** was achieved by using benzaldehyde at room temperature and anhydrous sodium sulfate. Filtration, concentration, and treatment of the crude imine directly with NaH and tetradecyl mesylate[16] led to the corresponding diether. The addition of HCl during the workup regenerated the primary amine and enabled the product **9a** to be isolated as the hydrochloride salt in 48% yield from **8a**. The optical rotation of **9a** (+10.7; *c* 0.8, $CHCl_3$) was in excellent agreement with that reported by Kokotos (+11.2; *c* 0.5, $CHCl_3$).[11] Finally, quaternization with methyl iodide revealed the cationic lipid **10a** in 89% yield (entry **1**, Table 1). Using a similar strategy, the 2*S*-isomers **9b** and **10b** were also generated (entry **2**, Table 1). Alternatively, when using *cis*-tetradec-11-enyl mesylate[17] the free amines **11a** and **11b** were isolated,m which were converted in a fashion similar to **12a** and **12b** (entries 3 and 4, Table 1), respectively. The use of oleyl mesylate[12] similarly generated the amines **13a** and **13b** and (2*R*)-DOTMA **1a** and (2*S*)-DOTMA **1b** (entries 5 and 6, Table 1). The optical rotation data for **1b** (−25.7; *c* 0.5, $CHCl_3$) were consistent with that reported by Felgner for the chloride salt of (2*S*)-DOTMA (−20; no *c* value, $CHCl_3$).[8] Overall this is a short, facile procedure, ideal for accessing saturated and unsaturated 1,2-dialkyloxy-3-trimethylammonium salts, which have hitherto received little attention in the literature despite their numerous applications in transfection studies.

Further studies were then undertaken to synthesize homochiral diether cationic lipids possessing an alternative group at the head position for applications in the synthesis of stereochemically defined functionalized lipids. Two strategies were explored: modification of the homochiral primary amine (such as compound **9a**) and the use of an alternative glycerol-based building block.

TABLE 1. Data for Formation of 1,2-Dialkyloxy-3-trimethylammonium Salts

entry	isomer	R	product; yield[a] (%)	salt; $[\alpha]_D$ [b]
1	2*R*	$C_{14}H_{29}$	**9a**; 48	**10a**; +37.7 (0.5)
2	2*S*	$C_{14}H_{29}$	**9b**; 50	**10b**; −41.5 (0.5)
3	2*R*	$C_{14}H_{27}$	**11a**; 51	**12a**; +14.0 (1)
4	2*S*	$C_{14}H_{27}$	**11b**; 48	**12b**; −12.0 (1)
5	2*R*	$C_{18}H_{35}$	**13a**; 44	**1a**; +26.4 (0.8)
6	2*S*	$C_{18}H_{35}$	**13b**; 50	**1b**; −25.7 (0.8)

[a] Yield for step a. [b] Optical rotation of 1,2-dialkyloxy-3-trimethylammonium salts in $CHCl_3$ at 23 °C, concentration *c* given in parentheses.

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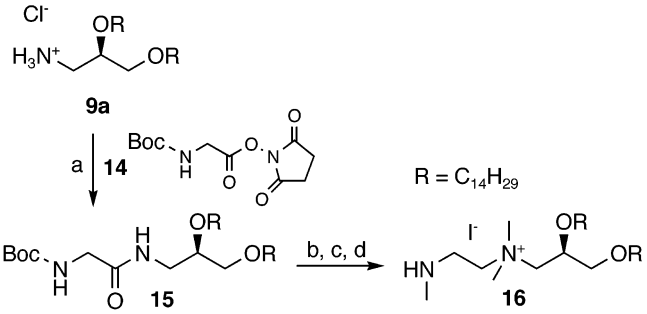
SCHEME 2[a]



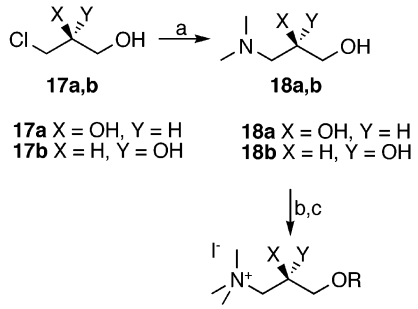
[a] Reagents and conditions: (a) $NaHCO_3$/dioxane (1:1), **14**, 96%; (b) $LiAlH_4$, THF, 18 h, 95%; (c) MeI, NaOH, 6 h, 64%; (d) TFA/CH_2Cl_2 (1:1), 97%.

An Eschweiler−Clark reductive methylation of salt **9a** with formaldehyde and formic acid, for subsequent quaternizsation with a third moiety, was first attempted.[18] However, an inseparable mixture of *N*-methylated products was generated. Use of Barbry's microwave accelerated reductive amination method also led to a mixture of products.[19] Alternative reductive amination procedures utilizing sodium cyanoborohydride similarly did not lead to the clean formation of the *N*,*N*-dimethylated compound. A route via the amide was then explored to generate an *N*-*β*-aminoethyl-substituted ammonium cation possessing a secondary amine moiety (Scheme 2). The salt **9a** was converted to the amine in situ and directly coupled to Boc-Glu-OSu **14** to give **15** in 96% yield. Subsequent reduction, methylation, and removal of the protecting group revealed **16**, *N*-methyl-*β*AE-DMRIE, a novel pH-sensitive cationic lipid in 57% overall yield from **9a**. This approach is particularly effective because it permits the synthesis of diverse functional lipids through the introduction of alternative functional groups at the terminal *N*-Me position.

An alternative approach was also investigated commencing from commercially available starting materials, (*S*)- or (*R*)-3-chloro-1,2-propanediol, **17a** and **17b**, respectively (Scheme 3). Conversion of **17a** to (*R*)-3-(*N*,*N*-dimethylamino)propane-1,2-diol (**18a**) in 89% yield was readily achieved through modification of Bhattacharya's method,[20] utilizing excess sodium hydroxide and dimethylamine hydrochloride to avoid the formation of bis-(2,3-dihydroxypropyl)-*N*,*N*-dimethylammonium chloride. Reaction with oleyl mesylate[12] under anhydrous basic conditions gave the dietherified product as previously reported.[1,4] Quaternization with a range of functionalized groups can then be carried out. However, for our purposes we quaternized the amines with methyl iodide to access **1a** and **1b** in near quantitative yield. We also prepared the novel C16:1 analogue **19**, via an analogous route, using *cis*-hexadec-11-enyl mesylate[17] (optical rotation data for **19a** +17.4, *c* 0.67 and **19b** −17.1, *c* 0.67).

In summary, two direct and versatile routes to homochiral dialkoxy alkylammonium cationic lipids from the chiral pool have been developed. From commercially available 3-amino-1,2-propane diol **8**, both enantiomers

SCHEME 3[a]



1a (2*R*)-DOTMA; X = OR, Y = H; R = $(CH_2)_8[Z]CH{=}CH(CH_2)_7CH_3$
1b (2*S*)-DOTMA; X = H, Y = OR; R = $(CH_2)_8[Z]CH{=}CH(CH_2)_7CH_3$
19a (2*R*); X = OR, Y = H; R = $(CH_2)_{10}[Z]CH{=}CH(CH_2)_3CH_3$
19b (2*S*); X = H, Y = OR; R = $(CH_2)_{10}[Z]CH{=}CH(CH_2)_3CH_3$

[a] Reagents and conditions: (a) NaOH (14.5 equiv), $HNMe_2$·HCl (11.5 equiv), 18 h, 89%; (b) NaH, oleyl mesylate, toluene, 61% for **1a**; (c) MeI, 95% for **1a**.

of DOTMA and chain length analogues were prepared, with transient protection of the NH_2 group as the corresponding imine as the key step. This route was then extended to access a novel headgroup functionalized lipid. Finally, a second route was developed by using the alternative chiral synthons (2*R*)- and (2*S*)-3-chloro-1,2-propanediol. These procedures are high yielding for reactions of this type and are highly versatile, as they can be adapted to generate cationic lipids with alternative headgroup moieties. The transfection activities of the optical isomers are currently under investigation, and the results will be published elsewhere.

Experimental Section

General Methods. The mesylates were prepared as previously reported.[12,16,17] Dietherification and quaternization of **18a** and **18b** was carried out as previously described.[1,4,8]

Representative Procedure: Preparation of (*R*)-2,3-Bis-(11*Z*-tetradecenyloxy)propanamine (11a). (2*R*)-3-Amino-1,2-propanediol (**8a**; 0.32 g, 3.50 mmol) and anhydrous Na_2SO_4 (2.49 g, 17.5 mmol) were stirred in anhydrous CH_2Cl_2/MeOH (10:1, 20 mL) at room temperature for 30 min. Benzaldehyde (0.37 g, 3.50 mmol) was added and stirring continued for 18 h. The mixture was then filtered and concentrated in vacuo to give the crude imine in quantitative yields. NaH (60%; 0.40 g, 10.5 mmol) was stirred in anhydrous THF (40 mL), the imine (0.63 g, 3.50 mmol) was added, and the resulting mixture was stirred for 4 h. 11*Z*-Tetradecenyl mesylate[17] (3.07 g, 10.5 mmol) was added and the mixture was heated at reflux for 72 h. The reaction was quenched with water (50 mL) and extracted with EtOAc (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was stirred in concentrated HCl/H_2O (1:1, 50 mL) and EtOH (50 mL) at room temperature for 6 h. The product was extracted with CH_2Cl_2 (2 × 75 mL) and the combined organic extracts washed with water (50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvents were removed in vacuo and the product purified by flash column chromatography (SiO_2; gradient $CHCl_2$ to $CHCl_2$/MeOH, 10:1) to give **11a** as an oil (0.43 g, 51%) $[\alpha]^{22}_D$ +7.4 (*c* 0.81, $CHCl_3$); ν_{max} ($CHCl_3$) 3380, 2934, 2856, 1460 cm^{-1}; ^1H NMR δ 0.95 (6H, t, J = 7.5 Hz), 1.27 (28H, m), 1.55 (4H, m), 2.04 (8H, m), 2.59 (2H, br s), 2.78 (1H, dd, J = 13.1 and 5.9 Hz), 3.12 (1H, dd, J = 13.1 and 3.2 Hz), 3.42−3.51 (6H, m), 3.69 (1H, m), 5.27−5.47 (4H, m); ^{13}C NMR δ 14.3, 20.5, 26.1, 27.1, 29.1, 29.3, 29.4−29.6 (signal overlap), 30.0, 32.5, 43.3, 70.3, 71.2, 71.7, 79.3, 129.3, 131.4; *m*/*z* HRMS calcd for $C_{31}H_{62}O_2N$ $(MH)^+$ 480.4781, found 480.4793; *m*/*z* (+ES) 481 (MH^+, 48%), 69 (100).

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Representative Procedure: (*R*)-1-Propanaminium, *N,N,N*-trimethyl-2,3-bis(11*Z*-tetradecenyl-oxy)-, Iodide (12a). The primary amine **11a** (100 mg, 0.19 mmol) and powdered sodium hydroxide (77 mg, 1.94 mmol) were stirred in iodomethane (2.0 mL) in a sealed tube at 90 °C for 18 h. After cooling, $CHCl_3$ (20 mL) was added and the mixture was washed with brine (20 mL) and dried ($MgSO_4$). The solvents were removed in vacuo to give **12a** as an oil (107 mg, 87%); $[\alpha]^{23}_D$ +14.0 (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 2934, 2856, 1464 cm^{-1}; ^1H NMR δ 0.93 (6H, t, J = 7.5 Hz), 1.25 (28H, m), 1.53 (4H, m), 2.02 (8H, m), 3.42 (4H, m), 3.49 (9H, s), 3.56−3.69 (3H, m), 4.04 (2H, m), 5.33 (4H, m); ^{13}C NMR δ 14.4, 20.5, 26.0, 26.2, 27.1, 29.7, 29.1, 29.2−30.0 (signal overlap), 55.3, 68.1, 69.3, 72.1, 73.5, 129.3, 131.5; *m/z* HRMS calcd for $C_{34}H_{68}O_2N$ $(M - I)^+$ 522.5250, found 522.5234; *m/z* (+ES) 523 ($M - I^+$, 100%).

(*R*)-[2,3-(Bis-tetradecyloxy-propyl-1-carbamoyl)methyl]-carbamic Acid *tert*-Butyl Ester (15). The amine salt **9a** (350 mg, 0.67 mmol) and Boc-Glu-OSu (**14**; 183 mg, 0.67 mmol) were stirred vigorously in sat. aqueous $NaHCO_3$ solution/dioxane (1:2, 21 mL) for 1 h. Water (50 mL) was added and the mixture extracted with EtOAc (3 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo to give **15** as an oil (410 mg, 96%); $[\alpha]^{22}_D$ +5.4 (*c* 3.0, $CHCl_3$); ν_{max} (film) 3315, 2922, 2850, 1694, 1658 cm^{-1}; ^1H NMR δ 0.86 (6H, t, J = 6.5 Hz), 1.24 (44H, m), 1.43 (9H, s), 1.51 (4H, m), 3.37−3.57 (9H, m), 3.70 (2H, d, J = 5.7 Hz), 5.12 (1H, m), 6.42 (1H, m); ^{13}C NMR δ 14.1, 22.7, 26.1, 26.2, 28.3, 29.3−29.6 (signal overlap), 30.0, 31.9, 40.7, 44.4, 70.3, 71.3, 71.9, 76.5, 80.0, 155.9, 169.3; *m/z* (+FAB) 642 (MH^+, 18%), 585 ($MH^+ - {}^tBu$, 100). Anal. Calcd for $C_{38}H_{76}O_5N_2$: C, 71.20; H, 11.95; N, 4.37. Found: C, 71.51; H, 12.24; N, 4.16.

(*R*)-(2,3-Bis-tetradecyloxy-propyl)-*N,N*-dimethyl-(2-*N*-methylamino-ethyl)ammonium, Iodide (16). The amide **15** (0.20 g, 0.31 mmol) was stirred in anhydrous THF at 0 °C. $LiAlH_4$ (1 M in THF, 1.25 mL, 1.25 mmol) was added dropwise and the resulting mixture was stirred vigorously for 24 h. The reaction was quenched by the addition of sat. aqueous NH_4Cl (2 mL). EtOAc (50 mL) was added and the mixture was washed with sat. aqueous $NaHCO_3$ solution (50 mL) and brine (50 mL). The organic extract was dried (Na_2SO_4) and concentrated in vacuo to give (*R*)-[2-(2,3-tetradecyloxy-propylamino)ethyl]carbamic acid *tert*-butyl ester as an oil (0.19 g, 95%), which was used without further purification; $[\alpha]^{22}_D$ +4.6 (*c* 1.5, $CHCl_3$); ν_{max} (film) 3333, 2923, 2853, 1717 cm^{-1}; ^1H NMR δ 0.84 (6H, t, J = 6.4 Hz), 1.22 (44H, m), 1.40 (9H, s), 1.49 (4H, m), 2.62−2.70 (4H, m), 3.17 (2H, m), 3.34−3.58 (7H, m), 4.97 (1H, m); ^{13}C NMR δ 14.0, 22.6, 26.2, 28.4, 29.3−30.2 (signal overlap), 30.3, 31.9, 40.2, 49.0, 50.8, 70.4, 71.7 (signal overlap), 72.1, 77.7, 79.0, 156.0; *m/z* (+ES) 627.86 (MH^+, 100%). Anal. Calcd for $C_{38}H_{78}O_4N_2$: C, 72.79; H, 12.54; N, 4.47. Found: C, 72.61; H, 12.46; N, 4.25.

(*R*)-[2-(2,3-Tetradecyloxy-propylamino)ethyl]carbamic acid *tert*-butyl ester (150 mg, 0.24 mmol) and powdered sodium hydroxide (20 mg, 0.48 mmol) were stirred in iodomethane (1 mL) at room temperature for 24 h. Excess CH_3I was removed in vacuo and CH_2Cl_2 (25 mL) was added to the resulting residue. Filtration of the insoluble inorganic salts and concentration of the filtrate in vacuo gave (*R*)-(2,3-bis-tetradecyloxy-propyl)[2-*tert*-butoxy-carbonyl-*N*-methylamino-ethyl]-*N,N*-dimethylammonium, iodide as a yellow oil (122 mg, 64%), which was used without further purification; $[\alpha]^{23}_D$ +11.2 (*c* 6.3, $CHCl_3$); ν_{max} (film) 2923, 2853, 1720 cm^{-1}; ^1H NMR δ 0.84 (6H, t, J = 7.0 Hz), 1.27 (44H, m), 1.42 (9H, s), 1.53 (4H, m), 3.00 (3H, s), 3.39−4.11 (19H, br m); *m/z* HRMS calcd for $C_{41}H_{85}O_4N_2$ $(M - I)^+$ 669.6509, found 669.6507.

(*R*)-(2,3-Bis-tetradecyloxy-propyl)-[2-*tert*-butoxycarbonyl-*N*-methylamino-ethyl]-*N,N*-dimethylammonium, iodide (40 mg, 0.05 mmol) was stirred in TFA/CH_2Cl_2 (1:1, 2 mL) at room temperature for 6 h. The solvents were removed in vacuo to give **16** (39 mg, 97%); $[\alpha]^{23}_D$ +5.4 (*c* 4.5, $CHCl_3$); ν_{max} (film) 3450, 2924, 2848, 1650 cm^{-1}; ^1H NMR 0.87 (6H, t, J = 6.6 Hz), 1.25 (44H, m), 1.54 (4H, m), 3.29−4.10 (22H, br m); ^{13}C NMR δ 14.0, 22.6, 25.9, 26.0, 29.4−29.9 (signal overlap), 31.9, 53.9, 68.1 (signal overlap), 69.6, 71.0, 72.1, 72.9; *m/z* HRMS calcd for $C_{36}H_{77}O_2N_2$ $[M - (I + TFA)]^+$ 569.5985, found 569.5980.

(*R*)-3-(*N,N*-Dimethylamino)propane-1,2-diol (18a). $HNMe_2 \cdot HCl$ (3.23 g, 39.6 mmol) and (2*S*)-3-chloro-1,2-propanediol (**17a**; 0.50 mL, 3.43 mmol) were added to sodium hydroxide (1.98 g, 49.5 mmol) in water (5 mL) at 0 °C in a sealed tube. The tube was sealed and the reaction mixture warmed to room temperature then stirred for 18 h. Water (5 mL) was added and the aqueous solution was washed with $CHCl_3$ (3 × 10 mL). The combined organic layer was dried over $MgSO_4$ and the solvent evaporated in vacuo to give **18a**[20] (0.33 g, 91%) as a yellow oil; $[\alpha]^{22}_D$ +17.1 (*c* 0.67, $CHCl_3$).

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Supporting Information Available: Experimental procedures and spectral data for compounds **1**, **9**, **10**, **13**, **18**, and intermediates toward **1** and **19**, and NMR spectra for compounds **10a**, **11a**, **12a**, **16**, and **19a** (and intermediates). This material is available free of charge via the Internet at http://pubs.acs.org.

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