Aziridines as Precursors for Chiral Amide-Containing Surfactants

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Received December 10, 1996[⊗]

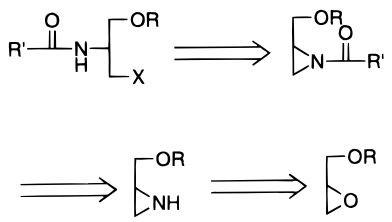
Optically active aziridines can be used as precursors in the synthesis of several enantiopure amide-containing surfactants. Acylation of the aziridines is a convenient method for both the activation of the aziridine ring and the introduction of the hydrocarbon chain. The regioselectivity of the ring-opening reactions using dibenzyl phosphate could be controlled by varying the reaction temperature. In this way both regioisomers of the phospholipid analogues could be obtained. In the course of these experiments, an unprecedented rearrangement of α-acylamino phosphotriesters was observed. A mechanism for this group exchange reaction was proposed based on the compared reactivities of related compounds and FT-IR spectroscopic data. Application of high pressures (12 kBar) for the ring opening of the activated aziridines with imidazole led to the efficient formation of the desired surfactant with complete regioselectivity.

Introduction

Following the discovery that phospholipid molecules can form tubular, rodlike, and even helical structures,[1] it has been demonstrated that chiral synthetic surfactants can also be used to construct similar superstructures.[2] The formation of these types of structures requires a high degree of organization within the aggregate in order to transfer the molecular chirality to the supramolecular level. Interconnecting the surfactant molecules by means of hydrogen bonding or $\pi-\pi$ stacking was shown to be most useful in achieving and stabilizing these highly organized aggregates.[2−4] In particular the formation of hydrogen-bonded chains of secondary amides, the so-called amide polymers, has been utilized successfully.[4]

A synthetic pathway for the preparation of amide-containing surfactants was developed in order to explore the use of amide functions in the construction of *chiral* aggregates. The synthesis of a series of new chiral surfactant molecules based on a C_3-skeleton having an amide-linked hydrocarbon chain on the C(2)-position was accomplished (Scheme 1). An ester or an ether group can be present on the primary position, and a variety of polar head groups can be introduced. A chiral precursor to which different hydrocarbon chains and polar head groups can be attached is required for the preparation of these lipids. In this respect the synthesis of phosphopeptides described by Okawa and co-workers is of interest.[5,6] These authors used the chemistry of aziridines to introduce both the amide and phosphate moiety in successive steps. The acylation of an aziridine function served both as a peptide-coupling reaction and as an activation step for the introduction of the phosphate group by opening of the aziridine ring. This particular reaction offers prospects for the synthesis of amide-containing surfactants. Starting from a suitable aziridine, only two reaction steps would suffice, in principle, for the introduction of both a hydrocarbon chain and a (protected) head group as depicted in Scheme 1 in a retrosynthetic manner.

Scheme 1



R = Acyl, Alkyl; R' = Alkyl; X = Polar head group

Synthesis of *N*-Acylaziridines

An established procedure for the synthesis of chiral aziridines was employed,[7−9] starting from the corresponding epoxides (Scheme 2). In this process the nucleophilic ring opening of the glycidyl derivatives **1** using sodium azide in 2-methoxyethanol/water[10] gave a mixture of the two regioisomeric azido alcohols in 77−92% yield. The distilled mixture of azido alcohols was transformed into only one stereoisomer of the aziridine, however, by reaction with triphenylphosphine. In this so-called Staudinger reaction,[11] both azido alcohols react

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1997.

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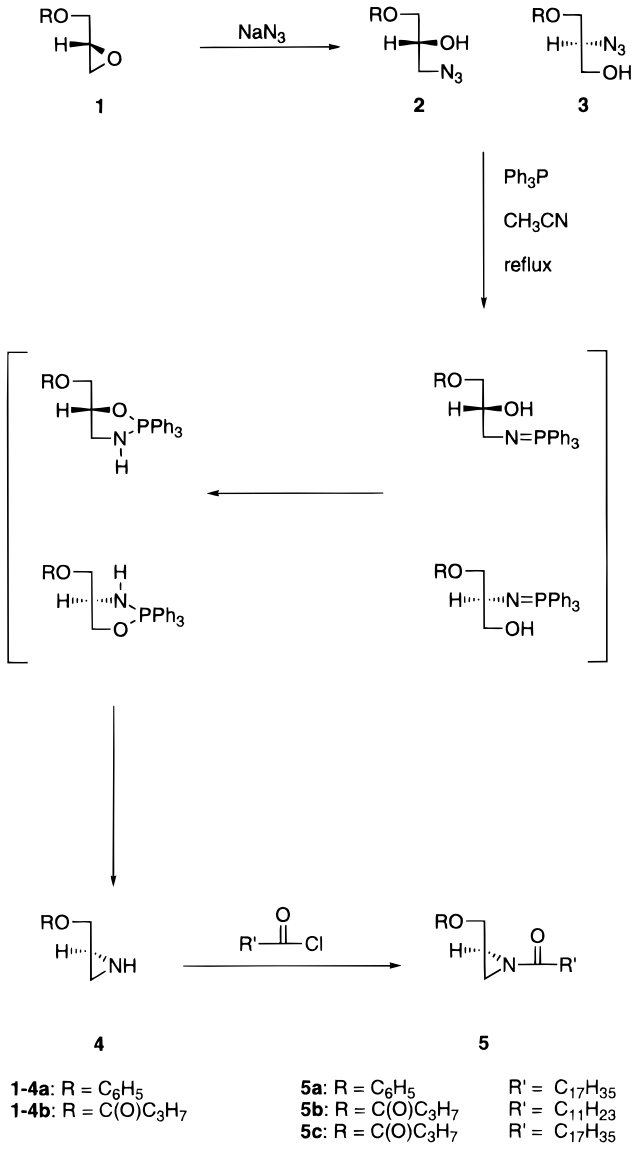
S0022-3263(96)02298-0 CCC: $14.00

Scheme 2



with triphenylphosphine with concomitant extrusion of nitrogen to form a regioisomeric mixture of phosphazo compounds. Intramolecular addition of the hydroxyl group leads to the formation of oxazaphospholidines, which in related cases, have been isolated and characterized.[12] Thermal cleavage of the P−N bond leads to the intramolecular substitution of the triphenylphosphine oxide group, resulting in the formation of an aziridine. The stereochemistry at either carbon atom in the aziridine ring is inverted compared with the stereochemistry at the starting epoxide. The inversion of the stereogenic center at C(2) takes place either during the epoxide ring opening or when the Ph_3PO group is displaced during the Staudinger reaction, depending on the site of the initial nucleophilic attack.

When the reaction was carried out on a gram scale, the aziridines **4** could be isolated in 55−75% yield.[13] The obtained (*S*)-(−)-aziridines **4** were acylated using different fatty acid chlorides in dichloromethane with triethylamine as the base. After column chromatography and crystallization from ethyl acetate, the acylated aziridines **5** were isolated as white solids in almost quantitative yields.

Ring Opening of *N*-Acylaziridines with Dibenzyl Phosphate

The synthesis of phosphopeptides by ring opening of acylated aziridines using either dibenzyl phosphate or phosphoric acid as the reagent has been reported to lead to the respective products in good yields (64−92%).[5] When dibenzyl phosphate was added to a solution of **5** in dichloromethane, a mixture of two products was obtained (Scheme 3). Both compounds were isolated using column chromatography and identified as the two regioisomers **6** and **7**, which arise from nucleophilic attack on either (a) the primary C(1) or (b) the secondary C(2) carbon atom. The ratio of **6** and **7** amounted to 1:1.

Different reaction temperatures were used with the aim of improving the regioselectivity of the ring opening. It was found that the product ratio could be changed from **6**:**7** = 1:1 at room temperature to **6**:**7** = 6:1 at −15 °C. At temperatures lower than −30 °C, no reaction took place. After column chromatography the two regioisomers could always be isolated in pure form in a combined yield of 70−80%.

Surprisingly, it was found that butyrate derivatives **6b**,**c**, after storage for several weeks, partially rearranged to give **7b**,**c** (Scheme 3, path c), whereas pure **6a** did not show any change during this period.[14] Application of longer reaction times or temperatures higher than room temperature did not change the product ratio, indicating that under the conditions of phosphorylation no rearrangement takes place.

This rearrangement of **6b**,**c** into **7b**,**c**, after their isolation, can be avoided by immediate removal of the benzyl groups by catalytic hydrogenation and subsequent conversion into the respective disodium salts **8b**,**c** (Scheme 4). Compound **8a** and compounds **9** were obtained from **6a** and **7**, respectively, in an analogous manner.

Mechanistic Aspects of the Rearrangement of α-Acylamino Phosphate Triesters

The rearrangement in α-acylamino phosphate triesters **6b**,**c** into **7b**,**c**, described in the preceding section, has no precedent in the literature. It is important to note that no byproducts of any sort were observed during this rearrangement. That the phenoxy derivative **6a** does not show this group exchange reaction is relevant for the mechanism. The findings suggest that a neighboring group participation of the butyrate ester group may be involved in the rearrangement. However, a nucleophilic displacement of the amido group by intramolecular attack of the ester carbonyl group either in an S_N1 or S_N2 fashion should lead to the formation of a dioxolenium ion, and as a consequence a product resulting from a shift of the butyrate to the C(2) carbon atom may be expected. No such product was observed, which makes the above

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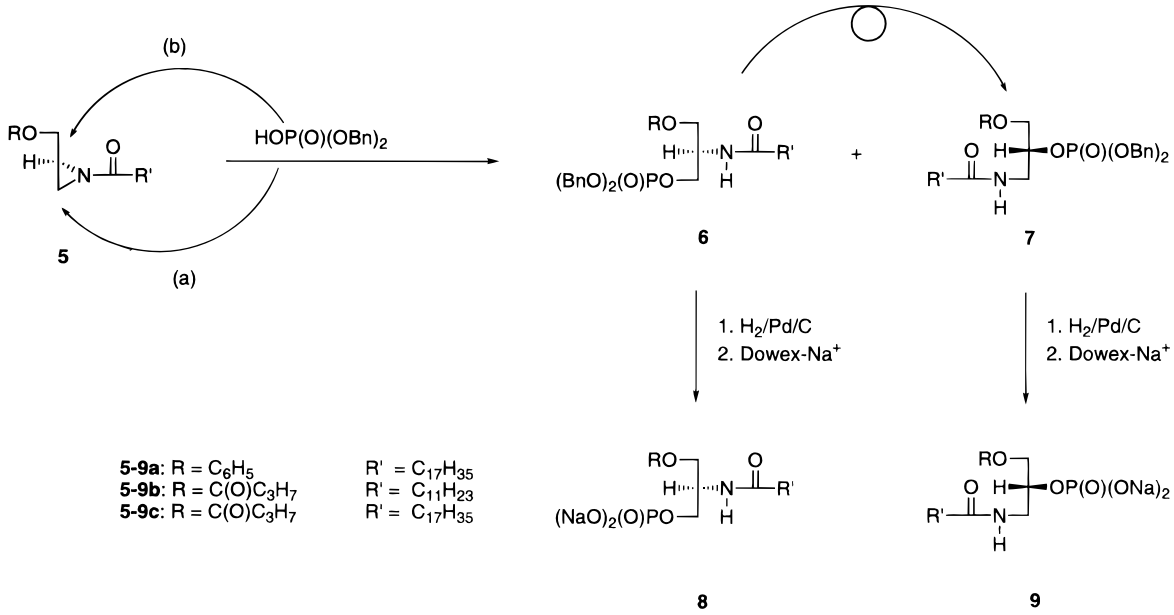
(13) When the reaction was carried out using larger quantities, the yield of isolated product decreased drastically, probably due to decomposition of the product during chromatography. Attempts to improve the yield of the reaction on a multigram scale, viz. by distillation of the reaction mixture or acid−base extraction, were not successful.

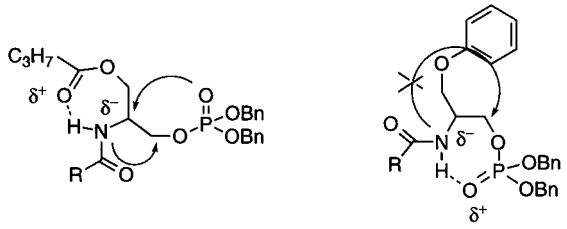
(14) The product isolated after the rearrangement gave the same optical rotation as the one obtained initially from the phosphorylation reaction.

Scheme 3



5-9a: R = C_6H_5 R' = $C_{17}H_{35}$
5-9b: R = $C(O)C_3H_7$ R' = $C_{11}H_{23}$
5-9c: R = $C(O)C_3H_7$ R' = $C_{17}H_{35}$

Scheme 4



6b, c **6a**

proposal less likely. A different role for the ester should therefore be considered. The following proposal for the rearrangement could account for the observations. It is assumed that the ester carbonyl group forms an intramolecular bond with the amide hydrogen (Scheme 4). In this manner the nucleophilicity of the amide nitrogen will be enhanced, and a displacement of the dibenzyl phosphate anion is now feasible *via* the formation of an intermediate aziridine ring. Subsequent ring opening of this three-membered ring by the dibenzyl phosphate anion, which is still favorable, then leads to the observed rearrangement products **7b**,**c**.

The phosphorylation of **5** is carried out under acidic conditions since a 2-fold excess of dibenzyl phosphate is used. This is in agreement with the proposed mechanism, because intermolecular protonation of the ester carbonyl will prevent the formation of hydrogen bonds and accordingly the rearrangement.

In order to substantiate the role of hydrogen bonding, FT-IR spectra of a chloroform solution of **6b** were recorded. This revealed the presence of two ester carbonyl vibrations at 1744 and 1729 cm^{-1}; the former is typical for a free ester function, and the latter is indicative of a hydrogen-bonded ester carbonyl.

Furthermore, the appearance of the amide I vibration at relatively high wavenumbers (1681 cm^{-1}) indicates the presence of an electron-rich amide group, supporting the increased nucleophilic character of the nitrogen atom. The FT-IR spectra of **6a** showed the amide I vibration at high wavenumbers (1681 cm^{-1}); however, in addition a broadening of the P=O vibration was also observed, suggesting a hydrogen bond between the N−H of the amide and the P=O of the phosphate group. The formation of such a hydrogen bond would again enhance the nucleophilic character of the amide nitrogen atom. Attack on the primary carbon atom bearing the phosphate group is not possible due to the induced *syn* orientation of the phosphate with respect to the amide, and no rearrangement takes place (Scheme 4).

Ring Opening of *N*-Acylaziridines with Imidazole

The nucleophilic ring opening of acylated aziridines **5a** and **5b** by imidazole was first carried out by using sodium imidazolate in DMF at 80 °C. After 2 days, TLC analysis of the mixture showed the formation of several products. In both cases **11** could be obtained in only 12−15% yield, after column chromatography.

In spite of the poor nucleophilicity of imidazole,[15] the use of this agent without the addition of a base was considered. A ring-opening reaction should proceed via the dipolar transition state **10** (Scheme 5). The formation of such a transition state will cause the solvent molecules to align their dipoles in a manner that electronically compensates the separation of charges. This will lead to a higher degree of organization and hence to a contraction of the volume of the reaction mixture. This negative volume of activation offers possibilities for the use of high pressure in accelerating product formation.[16] A series of experiments was performed using equimolar amounts of **5c** and imidazole in different solvents at 12 kBar.[17] It was found that the reaction in chloroform showed the highest degree of conversion. However, even after 48 h, only 50% of the starting material had been consumed. The reaction was still incomplete after 4 days

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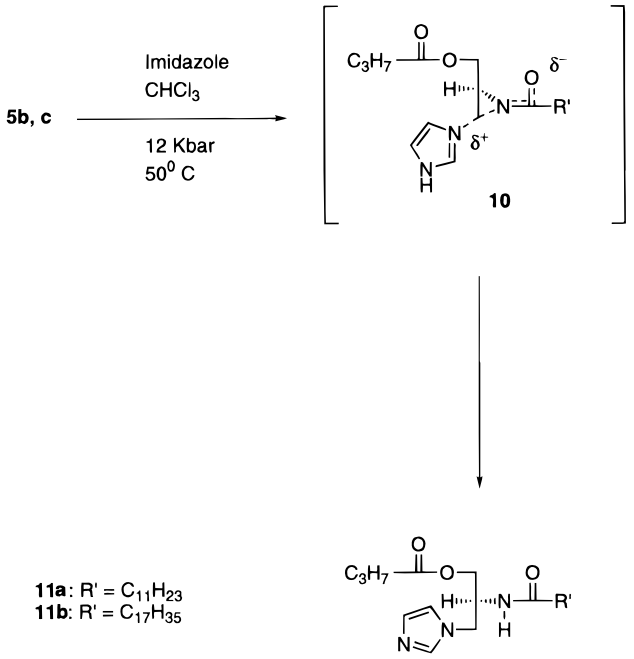
Scheme 5



at 50 °C. The use of higher imidazole concentrations improved the rate of conversion, whereas the use of higher concentrations of **5c** did not. These observations suggest that at higher pressures the precipitation of aziridine **5c** may limit the progress of the reaction. When the reaction was carried out with 2 equiv of imidazole in chloroform at 12 kBar and 55 °C for 2 days, the complete conversion of **5b**,**c** into the desired imidazolyl surfactant **11** was accomplished, without the formation of any byproducts. Column chromatography of the depressurized reaction mixture resulted in the isolation of **11** in 30−50% yield.[18]

Concluding Remarks

The results described in this paper show that optically active aziridines can be used as precursors in the synthesis of several enantiopure amide-containing surfactants. Acylation of the aziridines is a convenient method for both the activation of the aziridine ring and the introduction of the hydrocarbon chain. The regioselectivity of the ring-opening reactions using dibenzyl phosphate was found to be satisfactory when low reaction temperatures were applied, and even complete when imidazole was used.

In the course of the synthesis of these phospholipids, an unprecedented rearrangement of α-acylamino phosphotriesters was observed. A mechanism for this group exchange reaction was proposed on the basis of the compared reactivities of related compounds and FT-IR spectroscopic data.

The fact that both regioisomers of the phospholipid analogues could be obtained extends the possibility to study the relation between molecular structure and the expression of chirality on the supramolecular level in two closely related substrates.[19] A detailed study of the aggregation behavior of the chiral surfactants described above will be published elsewhere.

(18) A crude yield of ca. 90% was obtained. However, during the chromatographic procedure a considerable portion of the product was irriversibly bound to the silica.

Experimental Section

General. Most common procedures and instrumentation have been previously described.[7] (2*R*)-(−)-Glycidyl butyrate was purchased from Aldrich Chemical Co.; (*S*)-Glycidyl-3-nitrobenzenesulfonate was a kind gift from Mr. Z. van Eupen (LGSS, Nijmegen). Solvents were dried and distilled prior to use according to standard procedures.[20]

(2*R*)-1-Azido-3-phenoxypropan-2-ol (2a) and (2*S*)-2-Azido-3-phenoxypropan-1-ol (3a). To a solution of (*R*)-(phenoxymethyl)oxirane (**1a**)[13] (10.0 g, 66.7 mmol) in 130 mL of methoxyethanol/water (10/3, v/v) were added sodium azide (8.67 g, 133 mmol) and ammonium sulfate (10.7 g, 80 mmol). After the mixture was stirred for 16 h, water (50 mL) and diethyl ether (90 mL) were added. The layers were separated, and the water layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent and distillation under reduced pressure, a colorless oil was obtained in 92% yield (bp 107 °C, 0.04 mmHg). From GLC the ratio of **2a** and **3a** was determined to be 7.7:1: ^{1}H NMR ($CDCl_3$) **2a** δ 1.98 (s, 1H), 3.46 (d, 2H, J = 5.1 Hz), 4.03 (m, 2H), 4.13 (m, 1H), 6.76−7.37 (m, 5H); **3a** δ 1.98 (s, 1H), 2.77 (d, 2H, J = 5.2 Hz), 4.03 (m, 2H), 4.57 (m, 1H), 6.76−7.37 (m, 5H); IR (CCl_4) 3440, 3040, 2920, 2860, 2100, 1580 cm^{-1}.

(2*R*)-3-Azido-2-hydroxyprop-1-yl Butanoate (2b) and (2*S*)-2-Azido-3-hydroxyprop-1-yl Butanoate (3b). A mixture of **2b** and **3b** was synthesized starting from (2*R*)-(−)-glycidyl butyrate {$[\alpha]^{20}_D$ −26.3 (*c* 1.0, $CHCl_3$)} using the same procedure as described for compounds **2a** and **3a**. After distillation a colorless oil was obtained in 77% yield: bp 82 °C (0.05 mmHg); ^{1}H NMR ($CDCl_3$) **2b** δ 0.97 (t, 3H, J = 7.4 Hz), 1.67 (m, 2H), 2.69 (s, 1H), 2.34 (t, 2H, J = 7.4 Hz), 3.38 (m, 2H), 4.07 (m, 1H), 4.17 (m, 2H); **3b** δ 0.96 (t, 3H, J = 7.4 Hz), 1.67 (m, 2H), 1.80 (s, 1H), 2.34 (t, 2H, J = 7.4 Hz), 3.51 (d, 2H, J = 5.4 Hz), 3.77 (d, 2H, J = 4.9 Hz), 5.02 (m, 1H); IR (CCl_4) 3440, 2920, 2110, 1725 cm^{-1}; MS (CI^+) *m*/*z* 188 (M + 1), 170 (18), 145 (3).

(2*S*)-(+)-2-(Phenoxymethyl)aziridine (4a). A mixture of (*R*)-**2a** and (*S*)-**3a** (5.8 g, 30.5 mmol) was added to a solution of triphenylphosphine (8.4 g, 32.1 mmol) in acetonitrile (150 mL). The reaction mixture was stirred until nitrogen evolution had ceased and subsequently heated under reflux for 6 h. After removal of the solvent under reduced pressure, the mixture was dissolved in hexane/ethyl acetate (1/1, v/v) from which triphenylphosphine oxide crystallized. Column chromatography (silica, methanol/ethyl acetate = 5/95, v/v) yielded the pure aziridine as a colorless oil in 55% yield: $[\alpha]^{20}_D$ +5.63 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.7 (s, 1H), 1.64 (d, 1H, J = 3.4 Hz), 1.93 (d, 1H, J = 6.0 Hz), 2.46 (m, 1H), 3.80−4.27 (m, 2H), 6.84−7.38 (m, 5H); IR (CCl_4) 3300, 3050, 2950, 1590 cm^{-1}; MS (CI^+) *m*/*z* 299 (2M + 1), 150 (M + 1), 133 (26), 105 (11), 94 (13), 77 (5).

(2*S*)-(+)-Aziridin-2-ylmethyl Butanoate (4b). Compound **4b** was synthesized starting from a mixture of **2b** and **3b** using the same procedure as described for compound **4a**. A colorless oil was obtained in 64% yield: $[\alpha]^{20}_D$ +9.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.0 (t, 3H, J = 7.4 Hz), 0.9−1.0 (br s, 1H), 1.5−2.0 (m, 4H), 2.2−2.5 (m, 3H), 3.9 (*AA*′X, 1H), 4.2 (A*A*′X, 1H); IR (CCl_4) 3285, 1735 cm^{-1}.

(2*S*)-(−)-1-Octadecanoyl-2-(phenoxymethyl)aziridine (5a). At −10 °C a solution of stearoyl chloride (3.25 g, 10.7 mmol) in dichloromethane (100 mL) was added to a solution of **4a** (1.60 g, 10.7 mmol) and triethylamine (1.91 g, 18.8 mmol) in dichloromethane (100 mL). After 3 h the reaction mixture was washed with 10% (w/w) aqueous citric acid, and the organic layer was dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and crystallization from ethyl acetate gave **5a** as a white solid in 97% yield: mp 61 °C; $[\alpha]^{20}_D$ −25.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.8

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Hz), 1.25 (m, 28H), 1.65 (m, 2H), 2.22 (d, 1H, J = 3.3 Hz), 2.43 (t, 2H, J = 7.6 Hz), 2.46 (m, 1H), 2.85 (m, 1H), 4.02 (dd, 1H, J = 6.1 Hz, J = 10.4 Hz), 4.13 (dd, 1H, J = 10.4 Hz, J = 4.3 Hz), 6.91 (d, 2H, J = 8.2 Hz), 6.98 (t, 1H, J = 7.3 Hz), 7.27 (dd, 2H, J = 21.7 Hz, J = 8.2 Hz); IR (CCl_4) 3060, 2905, 2840, 1630, 1600 cm^{-1}; MS (CI^+) m/z 416 (M + 1), 322 (40), 267 (44), 150 (15). Anal. Calcd for $C_{27}H_{45}NO_2$: C, 78.02; H, 10.91; N, 3.37. Found: C, 77.34; H, 10.92; N, 3.21.

(2*S*)-(−)-2-[(Butyryloxy)methyl]-1-dodecanoylaziridine (5b). Compound **5b** was synthesized starting from **4b** and lauroyl chloride, using the same procedure as described for the synthesis of compound **5a**. A white solid was obtained in 95% yield: mp 30 °C; $[\alpha]^{20}_D$ −21.7 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 0.97 (t, 3H, J = 7.4 Hz), 1.25 (m, 16H), 1.65 (m, 2H), 1.68 (m, 2H), 2.11 (d, 1H, J = 3.3 Hz), 2.34 (t, 2H, J = 7.6 Hz), 2.41 (d, 1H, J = 5.8 Hz), 2.41 (t, 2H, J = 5.3 Hz), 2.70 (m, 1H), 3.99 (dd, 1H, J = 11.8 Hz, J = 6.6 Hz), 4.29 (dd, 1H, J = 11.8 Hz, J = 4.4 Hz); IR (CCl_4) 2905, 2840, 1735, 1620 cm^{-1}; MS (CI^+) m/z 326 (M + 1), 254 (4), 170 (11). Anal. Calcd for $C_{19}H_{35}NO_3$: C, 70.11; H, 10.84; N, 4.30. Found: C, 70.08; H, 10.91; N, 4.17.

(2*S*)-(−)-2-[(Butyryloxy)methyl]-1-octadecanoylaziridine (5c). Compound **5c** was synthesized starting from **4b** using the same procedure as described for the synthesis of compound **5a**. A white solid was obtained in 94% yield: mp 53.5 °C; $[\alpha]^{20}_D$ −30.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 0.97 (t, 3H, J = 7.4 Hz), 1.25 (m, 28H), 1.65 (m, 2H), 1.68 (m, 2H), 2.11 (d, 1H, J = 3.3 Hz), 2.34 (t, 2H, J = 7.6 Hz), 2.41 (d, 1H, J = 5.8 Hz), 2.41 (t, 2H, J = 5.3 Hz), 2.70 (m, 1H), 3.99 (dd, 1H, J = 11.8 Hz, J = 6.6 Hz), 4.29 (dd, 1H, J = 11.8 Hz, J = 4.4 Hz); IR (CCl_4) 2905, 2840, 1735, 1620 cm^{-1}; MS (FB^+) m/z 410 (M + 1), 818 (2M). Anal. Calcd for $C_{25}H_{47}NO_3$: C, 73.30; H, 11.56; N, 3.42. Found: C, 72.99; H, 11.48; N, 3.41.

Dibenzyl (2*R*)-3-Phenoxy-2-(octadecanoylamino)propan-1-yl Phosphate (6a) and Dibenzyl (2*R*)-3-Phenoxy-1-(octadecanoylamino)propan-2-yl Phosphate (7a). At room temperature a solution of dibenzyl phosphate (325 mg, 1.17 mmol) in dichloromethane was added to a solution of **5a** (405 mg, 0.98 mmol) in dichloromethane (50 mL). After 2.5 h the reaction mixture was washed using saturated aqueous $NaHCO_3$, and the layers were separated. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The mixture of **6a** and **7a** was obtained as a white solid in a total yield of 84%. The two regioisomers were separated using flash column chromatography (silica, ethyl acetate/hexane = 3:2, v/v). Compounds **6a** and **7a** were isolated in 43% and 29% yield, respectively. When the reaction was carried out at −15 °C, **6a** and **7a** were isolated in 70% and 15% yield, respectively. **6a**: $[\alpha]^{20}_D$ −23.4 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.29 (m, 28H), 1.72 (m, 2H), 2.14 (t, 2H, J = 7.6 Hz), 3.96−4.34 (m, 4H), 4.42 (m, 1H), 5.02 (d, 4H, J = 8.6 Hz), 6.22 (d, 1H, J = 7.8 Hz), 6.80−6.97 (m, 5H), 7.32 (br s, 10H); IR (CCl_4) 3015, 2925, 2850, 1675, 1240 cm^{-1}; MS (CI^+) m/z 694 (M + 1), 416 (46). **7a**: mp 44 °C; $[\alpha]^{20}_D$ +24.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 6.8 Hz), 1.17 (m, 28H), 1.80 (m, 2H), 2.09 (t, 2H, J = 7.6 Hz), 4.42 (m, 2H), 4.04 (d, 2H, J = 5.0 Hz), 4.66−4.83 (m, 1H), 5.04 (d, 4H, J = 8.4 Hz), 6.31 (t, 1H, J = 5.3 Hz), 6.80−6.97 (m, 5H), 7.27 (br s, 10H); IR (CCl_4) 3015, 2925, 2850, 1675, 1240 cm^{-1}; MS (CI^+) m/z 694 (M + 1), 416 (40).

Dibenzyl (2*R*)-3-(Butyryloxy)-2-(dodecanoylamino)propan-1-yl Phosphate (6b) and Dibenzyl (2*R*)-3-(Butyryloxy)-1-(dodecanoylamino)propan-1-yl Phosphate (7b). Compounds **6b** and **7b** were synthesized starting from **5b** using the same procedure as described for compounds **6a** and **7a**. The mixture was obtained as a colorless oil in a total yield of 81%. After column chromatography (silica, ethyl acetate/hexane = 3:1, v/v) **6b** and **7b** were isolated in 35% and 36% yield, respectively. When the reaction was carried out at −15 °C, **6b** and **7b** were isolated in 71% and 13% yield, respectively. **6b**: R_f = 0.37; $[\alpha]^{20}_D$ −4.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 0.92 (t, 3H, J = 7.4 Hz), 1.25 (m, 16H), 1.59 (m, 4H), 2.07 (t, 2H, J = 7.6 Hz), 2.24 (t, 2H, J = 7.6 Hz), 3.97−4.14 (m, 4H), 4.35−4.36 (m, 1H), 4.98−5.02 (m, 4H), 6.07 (d, 1H, J = 8.3 Hz), 7.35 (m, 10H); IR (CCl_4) 3300, 3200, 2950, 2850, 1740, 1680, 1260 cm^{-1}; MS (CI^+) m/z 326 (M − OPO(OBzl)$_2$), 277 (6), 254 (12), 238 (13), 198 (41). **7b**: R_f = 0.31; $[\alpha]^{20}_D$ +1.1 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 0.92 (t, 3H, J = 7.4 Hz), 1.29 (m, 16H), 1.63 (m, 4H), 2.07 (t, 2H, J = 7.6 Hz), 2.22 (t, 2H, J = 7.6 Hz), 3.31−3.38 (m, 1H), 3.56−3.62 (m, 1H), 4.08−4.20 (m, 2H), 4.59−4.53 (m, 1H), 5.03 (d, 4H, J = 8.7 Hz), 6.33 (t, 1H, J = 5.3 Hz), 7.35 (m, 10H); IR (CCl_4) 3300, 3200, 2950, 2850, 1740, 1680, 1260 cm^{-1}; MS (CI^+) m/z 326 (M − OPO(OBzl)$_2$), 277 (16), 254 (13), 240 (15), 198 (70). Anal. Calcd for $C_{33}H_{50}O_7NP{\cdot}2H_2O$: C, 61.95; H, 8.51; N; 2.19. Found: C, 62.03; H, 8.56; N, 2.19.

Dibenzyl (2*R*)-3-(Butyryloxy)-2-(octadecanoylamino)propan-1-yl Phosphate (6c) and Dibenzyl (2*R*)-3-(Butyryloxy)-1-(octadecanoylamino)propan-1-yl Phosphate (7c). Compounds **6c** and **7c** were synthesized starting from **5c** using the same procedure as described for compounds **6a** and **7a**. A colorless oil was obtained in 90% total yield. After column chromatography (silica, ethyl acetate/hexane = 3:1, v/v) **6c** and **7c** were isolated as colorless oils in 45% and 44% yield, respectively. When the reaction was carried out at −15 °C, **6c** and **7c** were isolated in 79% and 14% yield, respectively. **6c**: $[\alpha]^{20}_D$ −5.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 0.92 (t, 3H, J = 7.4 Hz), 1.25 (m, 28H), 1.59 (m, 4H), 2.07 (t, 2H, J = 7.6 Hz), 2.24 (t, 2H, J = 7.6 Hz), 3.97−4.14 (m, 4H), 4.35−4.36 (m, 1H), 4.98−5.02, (m, 4H), 6.07 (d, 1H, J = 8.3 Hz), 7.35 (m, 10H); IR (CCl_4) 3300, 3100−3000, 2905, 2840, 1735, 1675, 1260 cm^{-1}; MS (FAB^+) m/z 710 (M + Na^+), 688 (M + 1), 410 (100). **7c**: $[\alpha]^{20}_D$ +1.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 0.92 (t, 3H, J = 7.4 Hz), 1.29 (m, 28H), 1.63 (m, 4H), 2.07 (t, 2H, J = 7.6 Hz), 2.22 (t, 2H, J = 7.6 Hz), 3.31−3.38 (m, 1H), 3.56−3.62 (m, 1H), 4.08−4.20 (m, 2H), 4.53−4.59 (m, 1H), 5.03 (d, 4H, J = 8.7 Hz), 6.33 (t, 1H, J = 5.3 Hz), 7.35 (m, 10H); IR (CCl_4) 3300, 3100−3000, 2950, 2850, 1740, 1680, 1260 cm^{-1}; MS (CI^+) m/z 710 (M + Na^+), 688 (M + 1), 410 (100). Anal. Calcd for $C_{39}H_{62}NO_7P$: C, 68.10; H, 9.08; N, 2.04. Found: C, 67.77; H, 9.48; N, 2.08.

Disodium (2*R*)-3-Phenoxy-2-(octadecanoylamino)propan-1-yl Phosphate (8a). Phosphate triester **6a** (225 mg, 0.32 mmol) was dissolved in methanol (100 mL) and subjected to hydrogenation using palladium on carbon as a catalyst. After the uptake of hydrogen had ceased the catalyst was filtered off over a short RP-18 column. The solution was concentrated under reduced pressure to a volume of approximately 50 mL, and 20 mL of water was added. This mixture was passed through an ion-exchange column (Dowex 50W×2, sodium form) and the methanol evaporated under reduced pressure. After lyophilization, **8a** was isolated as a white solid in 89% yield: mp 145−147 °C; $[\alpha]^{20}_D$ −20.1 (*c* 1.0, $CHCl_3$); IR (AgCl) 3300, 3080, 2910, 2840, 1630, 1600, 1550 cm^{-1}; MS (FAB^+) m/z 580 (M + Na^+), 558 (M + 1). Anal. Calcd for $C_{27}H_{46}NO_6PNa_2{\cdot}1.5H_2O$: C, 55.47; H, 8.45; N, 2.40. Found: C, 55.41; H, 8.35; N, 2.32.

Disodium (2*R*)-3-Phenoxy-1-(octadecanoylamino)propan-1-yl Phosphate (9a). Compound **9a** was synthesized from **7a** using the same procedure as described for the synthesis of compound **8a** from **6a**. A white solid was obtained in 86% yield: mp 145−147 °C; $[\alpha]^{20}_D$ +6.1 (*c* 1.0, $CHCl_3$); IR (AgCl) 3500−3100, 3080, 2920, 2860, 1640, 1600, 1550 cm^{-1}; MS (FAB^+) m/z 580 (M + Na^+), 558 (M + 1). Anal. Calcd for $C_{27}H_{46}NO_6PNa_2{\cdot}2H_2O$: C, 54.63; H, 8.49; N, 2.36. Found: C, 54.57; H, 8.35; N, 2.24.

Disodium (2*R*)-3-Propanoyl-2-(dodecanoylamino)propan-1-yl Phosphate (8b). Compound **8b** was synthesized starting from **6b** using the same procedure as described for compound **8a**. A white solid was obtained in 78% yield: R_f = 0.33 (silica, $CH_3OH/H_2O/CHCl_3$ = 39/10/67, v/v/v); $[\alpha]^{20}_D$ −4.1 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3292, 2933, 2845, 1727, 1637, 1551 cm^{-1}; MS (FAB^+) m/z 469 (M + 2), 326 (M − OPO_3Na_2). Anal. Calcd for $C_{19}H_{36}NO_7PNa_2{\cdot}3H_2O$: C, 43.76; H, 7.73; N, 2.68. Found: C, 43.78; H, 7.90; N, 2.55.

Disodium (2*R*)-3-Propanoyl-1-(dodecanoylamino)propan-1-yl Phosphate (9b). Compound **9b** was synthesized starting from **7b** using the same procedure as described for compound **8a**. A white solid was obtained in 80% yield: R_f =

0.18 (silica, $CH_3OH/H_2O/CHCl_3$ = 39/10/67, v/v/v); $[\alpha]^{20}_D$ +1.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3400−3300, 2922, 2840, 1733, 1663, 1520 cm^{-1}; MS (FAB^+) *m/z* 469 (M + 2), 326 (M − OPO_3Na_2). Anal. Calcd for $C_{19}H_{36}NO_7PNa_2 \cdot {}^1/_2H_2O$: C, 47.89; H, 7.62; N, 2.94. Found: C, 47.73; H, 7.96; N, 2.37.

Disodium (2*R*)-3-Propanoyl-2-(octadecanoylamino)-propan-1-yl Phosphate 8c. Compound **8c** was synthesized starting from **6c** using the same procedure as described for compound **8a**. A white solid was obtained in 86% yield: R_f = 0.35 (silica, $CH_3OH/H_2O/CHCl_3$ = 39/10/67, v/v/v); $[\alpha]^{20}_D$ −5.2 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3292, 2933, 2845, 1727, 1637, 1551 cm^{-1}; MS (FAB^+) *m/z* 552 (M + Na^+), 574 (M + 1). Anal. Calcd for $C_{25}H_{48}NO_7PNa_2 \cdot 3H_2O$: C, 49.58; H, 7.99; N, 2.31. Found: C, 49.31; H, 8.08; N, 2.29.

Disodium (2*R*)-3-Propanoyl-1-(octadecanoylamino)-propan-1-yl Phosphate (9c). Compound **9c** was synthesized starting from **7c** using the same procedure as described for compound **8a**. A white solid was obtained in 84% yield: R_f = 0.20 (silica, $CH_3OH/H_2O/CHCl_3$ = 39/10/67, v/v/v); $[\alpha]^{20}_D$ +1.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$) 3400−3300, 2922, 2840, 1733, 1663, 1520 cm^{-1}; MS (FAB^+) *m/z* 552 (M + Na^+), 574 (M + 1). Anal. Calcd for $C_{25}H_{48}NO_7PNa_2$: C, 54.44; H, 8.77; N, 2.54. Found: C, 53.96; H, 9.22; N, 2.52.

(*R*)-(+)-Butyric Acid 2-(Dodecanoylamino)-3-imidazol-1-ylpropyl Ester (11a). A 10 mL ampoule was charged with a chloroform solution containing **5b** (215 mg, 0.66 mmol) and imidazole (90 mg, 1.32 mmol) and kept at 12 kbar for 4 days at 55 °C. After release of pressure the solvent was removed *in vacuo*, and the reaction mixture was subjected to flash column chromatography (silica, dichloromethane/ethanol/triethylamine = 92:7:1 v/v/v). After purification **11a** was isolated as a colorless oil in 30% yield: $[\alpha]^{20}_D$ +9.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 6.8 Hz), 0.98 (t, 3H, *J* = 7.4 Hz), 1.25 (m, 16H), 1.61 (m, 2H, *J* = 7.2 Hz), 1.66 (m, 2H, *J* = 7.4 Hz), 2.18 (t, 2H, *J* = 7.6 Hz), 2.35 (t, 2H, *J* = 7.4 Hz), 4.04 (dd, 1H, *J* = 14.8 Hz, *J* = 5.9 Hz), 4.17 (d, 2H, *J* = 5.0 Hz), 4.19 (dd, 1H, *J* = 14.2 Hz, *J* = 5.0 Hz), 4.40 (m, 1H, *J* = 3.3 Hz), 5.82 (d, 1H, *J* = 7.5 Hz), 6.94 (s, 1H), 7.08 (s, 1H), 7.49 (s, 1H); IR (CCl_4) 3300, 2910, 2850, 1735, 1670 cm^{-1}; MS (CI^+) *m/z* 394 (M + 1), 326 (21), 306 (21). Anal. Calcd for $C_{22}H_{39}N_3O_3 \cdot {}^1/_2H_2O$: C, 65.64; H, 10.01; N, 10.43. Found: C, 65.62; H, 10.08; N, 10.30.

(*R*)-(+)-Butyric Acid 2-(Octadecanoylamino)-3-imidazol-1-ylpropyl Ester (11b). Compound **11b** was synthesized starting from **6c** using the same procedure as described for compound **11a**. A white solid was obtained in 50% yield: mp 66−69 °C; $[\alpha]^{20}_D$ +5.9 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, *J* = 6.8 Hz), 0.98 (t, 3H, *J* = 7.4 Hz), 1.25 (m, 28H), 1.61 (m, 2H, *J* = 7.2 Hz), 1.66 (m, 2H, *J* = 7.4 Hz), 2.18 (t, 2H, *J* = 7.6 Hz), 2.35 (t, 2H, *J* = 7.4 Hz), 4.04 (dd, 1H, *J* = 14.8 Hz, *J* = 5.9 Hz), 4.17 (d, 2H, *J* = 5.0 Hz), 4.19 (dd, 1H, *J* = 14.2 Hz, *J* = 5.0 Hz), 4.40 (m, 1H, *J* = 3.3 Hz), 5.82 (d, 1H, *J* = 7.5 Hz), 6.94 (s, 1H), 7.08 (s, 1H), 7.49 (s, 1H); IR (CCl_4) 3300, 2910, 2850, 1735, 1670 cm^{-1}; MS (CI^+) *m/z* 478 (M + 1), 390 (50). Anal. Calcd for $C_{28}H_{51}N_3O_3 \cdot {}^1/_2H_2O$: C, 69.09; H, 10.77; N, 8.63. Found: C, 69.2; H, 10.35; N, 8.59.

Acknowledgment. The authors wish to thank J. W. Scheeren and R. W. M. Aben for valuable discussions and for the use of high-pressure equipment.

Supporting Information Available: ^1H-NMR spectra of compounds **2**−**4** and **6** (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO962298A