Iodocyclofunctionalization of (*Z*)-1-Trichloroacetimidoyloxyalk-2-enes and 3-Trichloroacetimidoyloxyalk-1-enes. Synthesis of (±)-*erythro*-Sphinganine Triacetate and (±)-*threo*-Sphinganine Triacetate

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(*Z*)-1-Trichloroacetimidoyloxyoctadec-2-ene, easily obtained from (*Z*)-octadec-2-en-1-ol, was iodocyclized with *N*-iodosuccinimide to give the 4-(1-iodohexadecyl)-2-trichloromethyl-4,5-dihydro-oxazole. From this compound, two routes were developed, either to pure (±)-*erythro*-sphinganine triacetate or to pure (±)-*threo*-sphinganine triacetate, respectively. The neutral cleavage of 4-(1-iodohexadecyl)-2-trichloromethyl-4,5-dihydro-oxazole gave the corresponding amide which, by treatment with Amberlyst A 26 (CO_3^{2-} form), afforded the *cis*-4-hydroxymethyl-5-pentadecyl-2-trichloromethyl-4,5-dihydro-oxazole together with a minor amount of *cis*-2-hydroxymethyl-3-pentadecylaziridine. After hydrolysis of the oxazole and full acetylation, (±)-*erythro*-sphinganine triacetate was obtained in 70% yield. On the other hand, acidic cleavage of the 4-(1-iodohexadecyl)oxazole 2-amino-3-iodo-octadecan-1-ol hydrochloride, which was directly treated with Amberlyst A 26 (AcO^- form). The product was acetylated and (±)-*threo*-sphinganine triacetate was recovered in 70% yield after chromatographic separation.

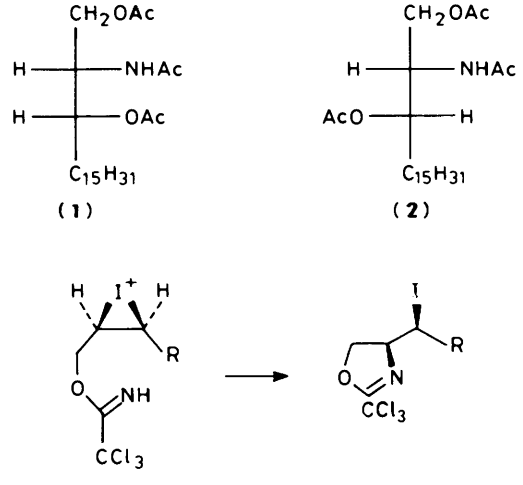
As an alternative, 3-trichloroacetimidoyloxyoctadec-1-ene was cyclized with *N*-iodosuccinimide to give a 20:80 *cis*:*trans* mixture of 4-iodomethyl-5-pentadecyl-2-trichloromethyl-4,5-dihydro-oxazoles. After ring cleavage, the corresponding ring-opened hydrochlorides were obtained. The mixture was then treated with Amberlyst A 26 (AcO^- form) and the product was directly acetylated. After silica gel chromatography, (±)-*threo*-sphinganine triacetate and (±)-*erythro*-sphinganine triacetate were obtained in good yield, in the ratio 80:20.

In the last few years an extensive amount of research has been directed towards cyclofunctionalization reactions, useful for the conversion of allylic alcohols or amines into polyfunctionalized moieties. The strategy of an intermediate ring formation allows us to achieve a high regio- and stereo-selection when two newly functionalized carbon centres are created.[1] Our previous investigation in this area involved conversion of allylic alcohols into trichloroacetimidates, followed by iodocyclization to the corresponding 4,5-dihydro-oxazoles, potential intermediates in the preparation of amino alcohols.[2] Concerning the stereochemistry of this reaction, we observed[2a] that, starting from 3-trichloroacetimidoalk-1-enes, diastereoisomeric *cis*:*trans* mixtures with high stereoselection were obtained, owing to the relative configuration of the newly formed chiral centre in respect to the pre-existing one. A pure *erythro* or *threo* configuration of the two newly formed centres was typically obtained, starting from primary allylic trichloroacetimidates, depending on the *anti*-attack to a *Z* or *E* iodonium-activated double bond.

The regiochemistry of this reaction could proceed through a 5-*exo* or 6-*endo* mode,[3] but five-membered rings were exclusively obtained from 3-trichloroacetimidoalk-1-enes; on the other hand, the iodonium-initiated cyclization of imidates on a *Z* or *E* disubstituted double bond will deserve further investigation.

Thus, owing to our interest in the synthesis of biologically active molecules, we report an application of this reaction to the synthesis of (±)-*erythro*-sphinganine triacetate (**1**) and (±)-*threo*-sphinganine triacetate (**2**).[4]

Sphinganine (2-amino-1,3-dihydroxyoctadecane) and sphingosine[5] are important components of cerebrosides, gangliosides, and sphingomyelins, and recently several papers have appeared, describing useful synthetic methods to obtain such compounds.[6] In planning the synthesis of sphinganines, we considered that a

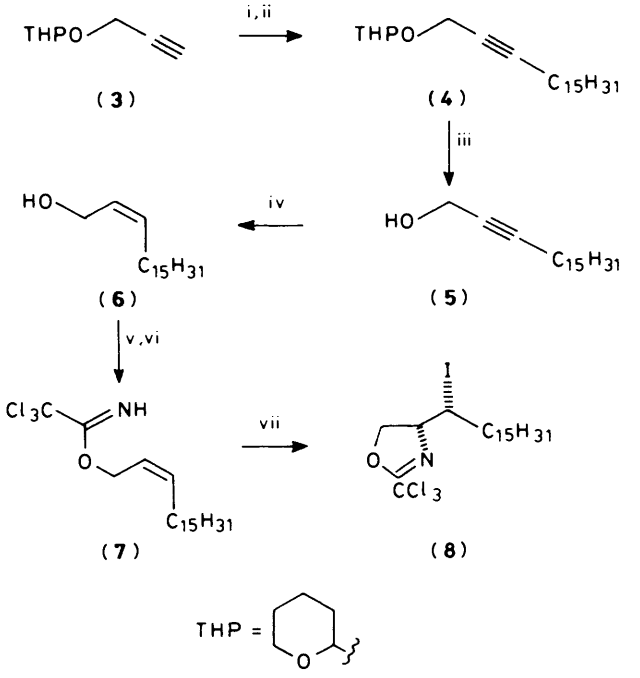


5-*exo* closure would be preferentially expected and an *anti*-attack to a *Z*-double bond would occur, leading to the *threo* C-2—C-3 relative configuration.

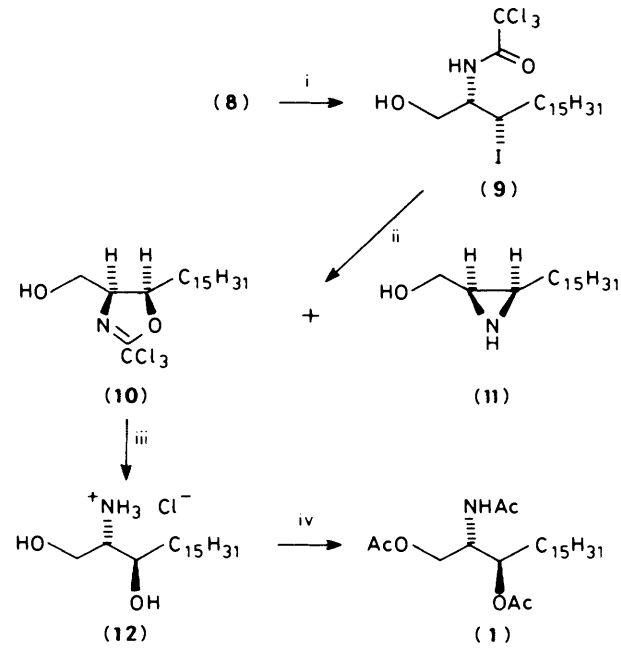
Thus, starting from the 4,5-dihydro-oxazole (**8**), two routes were developed, with total control of the relative configuration, and pure either (±)-*erythro*-sphinganine triacetate (**1**) or (±)-*threo*-sphinganine triacetate (**2**) was obtained, respectively, free from its diastereoisomer.

A convenient starting material to compound (**8**) was (*Z*)-octadec-2-en-1-ol (**6**) easily prepared in three steps: 2-(prop-2-ynyloxy)tetrahydropyran (**3**) was alkylated with iodopentadecane,[7] to afford the tetrahydropyranyl ether (**4**). After deprotection with Amberlyst H 15 in methanol[8] and reduction with hydrogen on Lindlar catalyst,[9] (*Z*)-octadec-2-en-1-ol (**6**) was

obtained in good yield. The conversion into the corresponding trichloroacetimidate (**7**) was accomplished in 90% yield on treatment of alcohol (**6**) with a catalytic amount of NaH, followed by addition of trichloroacetonitrile at 0 °C in tetrahydrofuran (THF).[10] The iodocyclization of imidate (**7**) was performed in $CHCl_3$ with *N*-iodosuccinimide (NIS) for 12 h at room temperature, and purification of the product by flash chromatography afforded the 4,5-dihydro-oxazole (**8**) in 90% yield (Scheme 1). The formation of a five-membered ring was established by i.r. spectroscopy, whereby the absorption at 1 650 cm^{-1} could be used as a diagnostic feature for 2-trichloromethyl-4,5-dihydro-oxazoles.[11,2a]



Scheme 1. *Reagents and conditions:* i, LDA, THF, 3 h, room temp.; ii, $C_{15}H_{31}I$, THF, 12 h, 55 °C; iii, Amberlyst H 15, MeOH, 3 h, room temp.; iv, $H_2/Pd/CaCO_3$, AcOEt, 6 h, room temp.; v, NaH (0.1 equiv.), THF, 1 h, 0 °C; vi, CCl_3CN, THF, 1 h, 0 °C; vii, NIS, $CHCl_3$, 12 h, room temp.



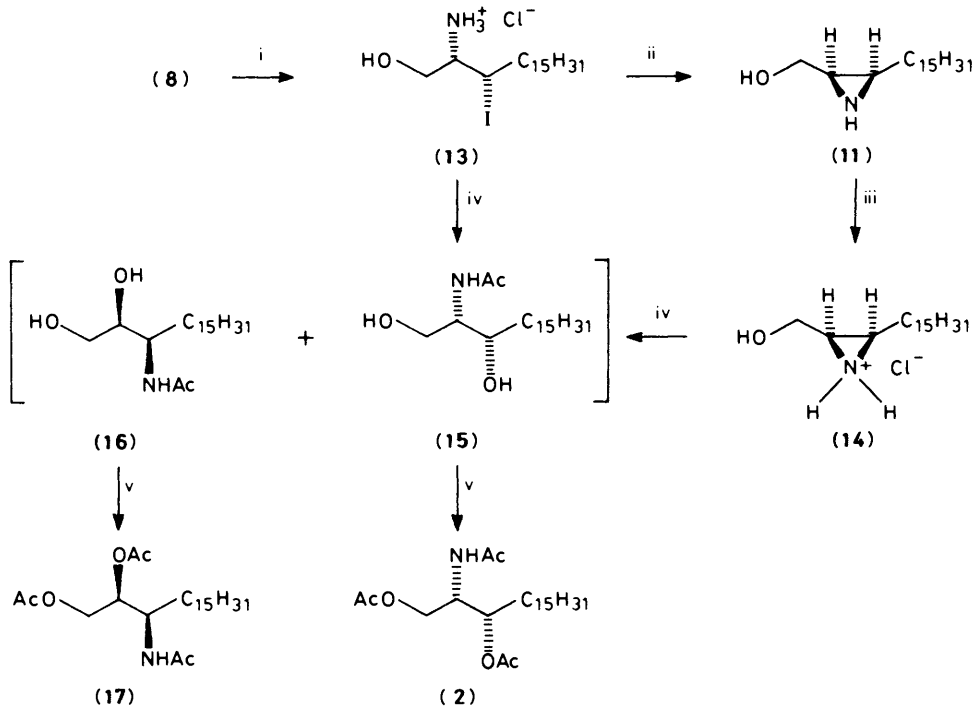
Scheme 2. *Reagents and conditions:* i, acetone water, 18 h, reflux; ii, Amberlyst A 26 (CO_3^{2-} form), benzene, 1 h, reflux; iii, 2M-HCl, 2 h, room temp.; iv, Ac_2O–pyridine, 18 h

Starting from the 4,5-dihydro-oxazole (**8**), a route to the pure (±)-*erythro*-sphinganine (**1**) was devised, as reported in Scheme 2. On hydrolysis in water at room temperature,[12] the 4,5-dihydro-oxazole (**8**) gave the corresponding amide (**9**) in quantitative yield; this product was then treated with Amberlyst A 26 (CO_3^{2-} form) in refluxing methanol for 1 h. Two products were obtained, in a 70:30 ratio, and were easily separated by flash chromatography. The major component was identified as the *cis*-4-hydroxymethyl-4,5-dihydro-oxazole (**10**). Its regiochemistry was assigned from the i.r. absorption at 1 660 cm^{-1}, while the stereochemistry was proven as *cis* by the coupling constant (J_{4H-5H} 9 Hz) observed in the ^1H n.m.r. spectrum.[13]

The minor component (**11**) corresponded to the *cis*-aziridine structure, as determined from its spectroscopic and mass spectral data. The stereochemistry of the *cis* and *trans* diastereoisomeric aziridines, the last one independently obtained by another chemical pathway, was determined from their ^1H n.m.r. spectra. The larger deshielding and coupling constants (δ_H 2.1, $\Delta\nu/2$ 20 Hz) of the ring protons of compound (**11**), in comparison with the values (δ_H 1.8, $\Delta\nu/2$ 12 Hz) observed for the *trans* isomer, were in agreement with a *cis*-structure.[13] This assignment was further confirmed by the ^{13}C n.m.r. spectra of the two aziridines, where the CH_2O signal of the *cis*-isomer (**11**) was more deshielded with respect to the *trans* one (δ_C 61.8 *vs.* δ_C 63.4).[14] Hydrolysis of the oxazole (**10**), performed with 2M-HCl in MeOH, and direct acetylation of the salt (**12**) with acetic anhydride and pyridine afforded, after silica gel chromatography and recrystallization of the product from light petroleum, (±)-*erythro*-sphinganine triacetate (**1**) in 70% yield. The stereostructure of compound (**1**) was proven by the total agreement of the m.p. (89—91 °C; lit.,[6d] 90—92 °C) and i.r. spectrum with the data reported for the natural racemic compound.[6d]

Starting from 4,5-dihydro-oxazole (**8**), a modified approach (Scheme 3) was required to synthesize (±)-*threo*-sphinganine triacetate (**2**). Thus acidic hydrolysis of (**8**) with 2M-HCl in methanol gave the *threo*-salt (**13**) in quantitative yield. In order to maintain the *threo* configuration in the sphinganine, a double inversion at C-3 must occur, through the formation of an intermediate aziridine.

By treatment of compound (**13**) with Amberlyst A 26 (CO_3^{2-} form) in methanol for 1 h at room temperature, the corresponding aziridine was isolated simply by filtering off the resin, and was identical with the aziridine (**11**) previously described, as shown by ^1H and ^{13}C n.m.r. data. The corresponding hydrochloride (**14**) was then obtained on treatment with an equimolar amount of HCl. To the salt dissolved in stirred methanol was added an excess of Amberlyst A 26 (AcO^- form) in methanol at room temperature; two acetamides, (**15**) and (**16**) (i.r., 1 650 and 1 510 cm^{-1}), were obtained in a 70:30 ratio, and the crude mixture was directly acetylated. The same result was reached on refluxing (**13**) in methanol for 12 h with Amberlyst A 26 (AcO^- form). After full acetylation, the components were separated by silica gel chromatography, affording as the major product the (±) silica gel chromatography, affording as the major product the (±)-*threo*-sphinganine triacetate (**2**) in 70% yield. Its m.p. (65—66 °C; lit.,[6d] 65—66 °C) was in complete agreement with the data reported in the literature, and the i.r. spectrum was



Scheme 3. *Reagents and conditions:* i, 2M-HCl, acetone, 2 h, room temp.; ii, Amberlyst A 26 (CO_3^{2-} form), MeOH, 1 h, room temp.; iii, 2M-HCl; iv, Amberlyst A 26 (AcO^- form), benzene, 12 h, reflux; v, Ac_2O–pyridine, 18 h

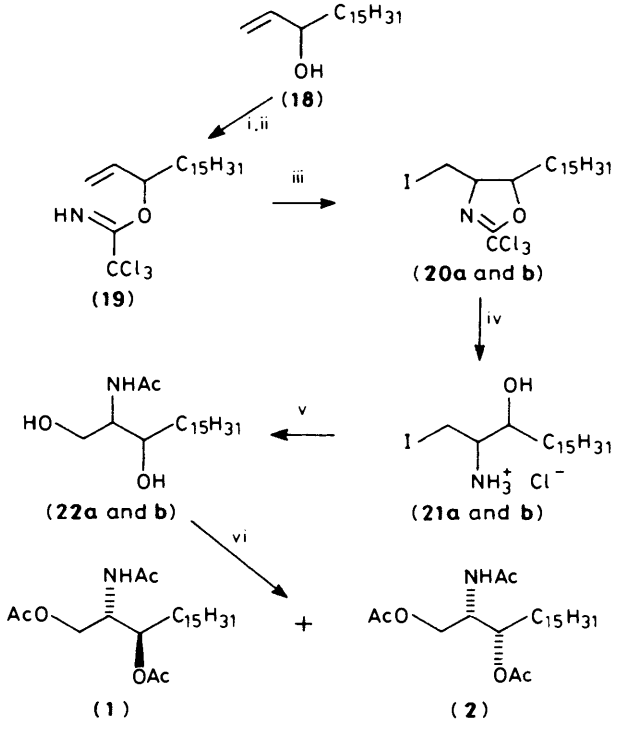
identical with that reported in the literature for (±)-*threo*-sphinganine triacetate (**2**).[6d]

The minor component was identified as the regioisomer *threo*-3-amino-octadecane-1,2-diol triacetate (**17**), on the basis of spectroscopic and mass spectral data. The structural assignment of compound (**17**) and a further confirmation of the structure of compound (**2**) were accomplished on the basis of selective ^1H n.m.r decoupling experiments performed at 300 MHz (see Experimental section).

From a comparison of the ^1H n.m.r. spectra of (±)-*erythro*-sphinganine triacetate (**1**) and (±)-*threo*-sphinganine triacetate (**2**), performed at 300 MHz in $CDCl_3$, the most meaningful difference was in the difference in value for $J_{2H\ 3H}$ (5.5 Hz for the *erythro*-isomer and 3.5 Hz for the *threo*-isomer). Accordingly, these data were consistent with a preferential *anti*-arrangement for the *erythro*-isomer and a preferential *gauche*-arrangement for the *threo*-isomer, at variance with data reported for 2,3-diacetoxybutanes.[15]

A further application of the imidate pathway to the synthesis of (±)-sphinganines proceeded from octadec-1-en-3-ol (**18**), readily prepared as described in the literature.[16] The corresponding trichloroacetimidate (**19**) was cyclized with NIS in $CHCl_3$ at room temperature to give a diastereoisomeric mixture of 4,5-dihydro-oxazoles (**20a**) and (**20b**) in a *cis*:*trans* ratio of 20:80, as determined by the ^{13}C n.m.r. spectrum (δ_C *cis*, 87.1, 69.7; δ_C *trans* 89.5, 71.4).[14]

After ring cleavage of compounds (**20a** and **b**) with 2M-HCl in acetone, the corresponding salts (**21a** and **b**) were quantitatively obtained. Without further purification the mixture (**21a** and **b**) was refluxed in benzene with Amberlyst A 26 (AcO^- form). The diastereoisomeric amides (**22a** and **b**) were obtained, and were directly acetylated, and the mixture was easily separated on silica gel chromatography to afford in good yield, (±)-*threo*-sphinganine triacetate (**2**) (m.p. 65—66 °C; lit.,[6d] 65—66 °C) and (±)-*erythro*-sphinganine triacetate (**1**) (m.p. 89—91 °C lit.,[6d] 90—92 °C) in the ratio 80:20 (Scheme 4).



Scheme 4. *Reagents and conditions:* i, n-BuLi (catalytic amount), THF, 20 min, room temp.; ii, CCl_3CN, THF, 1 h, 0 °C; iii, NIS, $CHCl_3$, 12 h, room temp.; iv, 2M-HCl, 1 h, room temp.; v, Amberlyst A 26 (AcO^- form), benzene, 6 h, reflux; vi, Ac_2O–pyridine, 18 h, room temp.

Experimental

THF was distilled from $LiAlH_4$ or sodium–benzophenone immediately prior to use. All reactions involving organometallic

reagents were carried out under argon. M.p.s (Pyrex capillary) were determined on a Buchi 510 hot-stage apparatus and are uncorrected. I.r. spectra were obtained with a Perkin-Elmer Model 682 spectrophotometer either on films or, for solids, on Nujol mulls. ^{1}H N.m.r. spectra were recorded on either a Varian EM 390 (90 MHz) or a Bruker XP 300 (300 MHz) spectrometer with tetramethylsilane as internal reference. ^{13}C N.m.r. spectra (20 MHz) were recorded using a Varian FT 80-A spectrometer. All chemical shifts were measured relative to tetramethylsilane (δ 0). Mass spectra were obtained with a double-focusing Varian MAT 112 instrument at an ionizing voltage of 70 eV. Mass spectral data are tabulated as *m/z* values. Analytical g.l.c. was carried out on a Carlo Erba capillary gas chromatograph (Fractovap 4160) equipped with a SE-52 flexible glass capillary column (25 m × 0.3 mm i.d.; carrier gas He; P_{He} 0.6 kg cm^{-2}). Chromatograms, peak areas, and retention times were obtained by using a Perkin-Elmer Sigma 10 data processor. T.l.c. and column chromatography were carried out on Kieselgel GF_{254} (Merck). Solvent ratios are in volumes before mixing. Solutions were dried over anhydrous magnesium sulphate.

2-(*Prop*-2-*ynyloxy*)*tetrahydropyran* (**3**).—This compound was prepared as described in ref. 8: b.p. 67 °C/10 mmHg (lit.,[17] 63—65 °C/9 mmHg); $\delta_H(CDCl_3)$ 1.3—3.2 (6 H, m), 2.25 (1 H, t, *J* 2 Hz), 3.3—4.0 (2 H, m), 4.15 (2 H, d, *J* 5 Hz), and 4.8 (1 H, brs).

2-(*Octadec*-2-*ynyloxy*)*tetrahydropyran* (**4**).—To a solution of *N*,*N*-di-isopropylamine (5.15 g, 50 mmol) in dry THF (50 ml) at 0 °C under argon was added n-BuLi (1.8M in n-hexane; 27.8 ml, 50 mmol) and the solution was stirred for 1 h. Then a solution of compound (**3**) (7.0 g, 50 mmol) in dry THF (20 ml) was added dropwise to the clear solution at 0 °C during 1 h, and after 3 h a solution of 1-iodopentadecane (16.9 g, 50 mmol) in dry THF (20 ml) was slowly added dropwise, and the reaction mixture was then heated at 55 °C for 12 h. After the usual work-up, the solvent was evaporated off under reduced pressure and the residue was chromatographed through silica gel, with cyclohexane–AcOEt (98:2) as eluant, and compound (**4**) was obtained (12.1 g, 75%) as a clear oil; $\delta_H(CDCl_3)$ 0.85 (3 H, t), 1.3 (26 H, m), 1.7 (6 H, m), 1.9—2.5 (2 H, m) 3.2—4.1 (2 H, m), 4.2 (2 H, t, *J* 2 Hz), and 4.8 (1 H, m).

Octadec-2-*yn*-1-*ol* (**5**).—To a solution of compound (**4**) (10.5 g, 30 mmol) in MeOH (80 ml) was added Amberlyst H 15 (1 g, 4 mequiv. g^{-1}), and the mixture was stirred for 3 h at 40 °C. The resin was then filtered off and the solvent was removed under reduced pressure, to give the alcohol (**5**) in a quantitative yield as a low melting solid; $\nu_{max.}$ 3 300 and 2 110 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (3 H, t), 1.3 (26 H, m), 1.8—2.4 (2 H, m), 2.25 (1 H, br s, OH), and 4.2 (2 H, t, *J* 2 Hz).

(Z)-*Octadec*-2-*en*-1-*ol* (**6**).—To a solution of the ynol (**5**) (5.3 g, 20 mmol) in AcOEt (15 ml) was added Lindlar catalyst ($Pd/CaCO_3$; 600 mg) and the suspension was stirred under H_2 (4 atm) for 6 h. After filtration and removal of the solvent under reduced pressure, the residue was chromatographed on silica gel with cyclohexane–AcOEt (8:2) as eluant, and enol (**6**) was obtained (4.3 g, 80%) as a low melting solid; $\nu_{max.}$ 3 330 cm^{-1}; $\delta_H(CDCl_3)$ 0.85 (3 H, t), 1.25 (26 H, m) 1.8—2.1 (2 H, m), 2.75 (1 H, br s, OH), 4.15 (2 H, d, *J* 5 Hz), and 5.2—5.65 (2 H, m); $\delta_C(CDCl_3)$ 133.0, 128.6, 62.9, 58.5, 32.9, 32.0, 30.7, 30.0, 29.8, 29.6, 29.5, 29.4, 29.0, 27.5, 27.0, 25.9, 22.8, and 14.1.

1-*Trichloroacetimidoyloxyoctadec*-2-*ene* (**7**).—A solution of (*Z*)-octadec-2-en-1-ol (**6**) (5.4 g, 20 mmol) in dry THF (70 ml) under argon was added at 0 °C to a stirred suspension of NaH (50% in mineral oil; 400 mg, 8 mmol; previously was washed with dry pentane) in dry THF (15 ml). After 1 h the resulting mixture was added dropwise at 0 °C to a solution of trichloroacetonitrile (4.8 g, 33 mmol) in dry THF (30 ml). The solution was stirred for 1.5 h at room temperature, and concentrated under reduced pressure, and then pentane (50 ml) containing MeOH (3 ml) was added to the stirred residue. Successive filtration, evaporation of the solvent under reduced pressure, and silica gel chromatography of the residue with cyclohexane–AcOEt (95:5) as eluant gave the imidate (**7**) (5.8 g, 70%) as a clear oil; $\nu_{max.}$ 3 340 and 1 660 cm^{-1}; $\delta_H(CDCl_3)$ 0.85 (3 H, t), 1.25 (26 H, m), 1.8—2.35 (2 H, m), 4.75 (2 H, d, *J* 6 Hz), 5.7 (2 H, m), and 8.2 (1 H, br s, NH); $\delta_C(CDCl_3)$ 136.0, 122.4, 65.1, 29.9, 29.5, 28.7, 28.6, 28.5, 28.4, 27.4, 26.8, 26.7, 22.5, and 13.9.

threo-4-(1-*Iodohexadecyl*)-2-*trichloromethyl*-4,5-*dihydro-oxazole* (**8**).—To a stirred solution of the imidate (**7**) (6.2 g, 15 mmol) in $CHCl_3$ (70 ml) was added NIS (3.6 g, 16 mmol) at room temperature. After 6 h the reaction mixture was diluted with $CHCl_3$ (80 ml) and washed successively with 10% aqueous $Na_2S_2O_3$ and water; the organic layer was separated and the solvent was removed under reduced pressure. After silica gel chromatography of the residue with cyclohexane as eluant, the *oxazole* (**8**) was obtained (7.3 g, 90%) as a clear oil; $\nu_{max.}$ 1 655 cm^{-1}; $\delta_H(CDCl_3)$ 0.85 (3 H, t), 1.25 (26 H, m,), 1.6—2.2 (2 H, m), and 3.8—4.8 (4 H, m); $\delta_C(CDCl_3)$ 75.4, 71.9, 39.1, 34.7, 31.9, 29.7, 29.5, 29.4, 28.7, 22.7, and 14.1 (Found: C, 36.1; H, 5.4; N, 2.0. $C_{20}H_{35}Cl_3INO$ requires C, 36.09; H, 5.30; N, 2.10%).

threo-3-*Iodo*-2-*trichloroacetamido-octadecan*-1-*ol* (**9**).—To a solution of the dihydro-oxazole (**8**) (5.4 g, 10 mmol) in acetone (100 ml) was added water (10 ml) and the mixture was refluxed for 18 h. The solvent was then evaporated off and the residue was chromatographed through silica gel with cyclohexane–AcOEt (95:5) as eluant to give the *amide* (**9**) (4.4 g, 80%) as an oil; $\nu_{max.}$ 3 380, 1 710, and 1 510 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (3 H, t), 1.3 (26 H, m), 1.6—1.9 (2 H, m), 3.2 (1 H, br s, OH), 3.5—4.1 (3 H, m), 4.4—4.8 (1 H, m), and 7.2 (1 H, d, *J* 8 Hz, NH); $\delta_C(CDCl_3)$ 65.0, 56.1, 40.1, 38.2, 31.9, 29.7, 29.4, 28.7, 26.9, 22.7, and 14.1 (Found: C, 35.1; H, 5.4; N, 2.1. $C_{20}H_{37}Cl_3INO_2$ requires C, 35.14; H, 5.46; N, 2.05%).

cis-4-*Hydroxymethyl*-5-*pentadecyl*-2-*trichloromethyl*-4,5-*dihydro-oxazole* (**10**).—The amide (**9**) (5.6 g, 10 mmol) was dissolved in dry benzene (20 ml), Amberlyst A 26 (CO_3^{2-} form) (10 g; ~3.8 mequiv. g^{-1}) was added, and the suspension was refluxed for 1 h. The resin was then filtered off, the solvent was removed under reduced pressure, and the residue was chromatographed through silica gel, with cyclohexane–AcOEt (9:1) as eluant, to give the *oxazole* (**10**) (2.0 g, 48%) as an oil; $\nu_{max.}$ 3 300 and 1 655 cm^{-1}; $\delta_H(CDCl_3)$ 0.85 (3 H, t), 1.3 (26 H, m), 1.6—2.0 (2 H, m), 3.3—4.3 (4 H, m, *J* 9 Hz), and 4.8 (1 H, br s, OH); $\delta_C(CDCl_3)$ 86.3, 73.2, 63.6, 34.7, 32.0, 29.7, 29.4, 24.4, 22.7, and 14.1 (Found: C, 56.1; H, 8.4; N, 3.3. $C_{20}H_{36}Cl_3NO_2$ requires C, 56.01; H, 8.46; N, 3.27%).

Further elution gave the *aziridine* (**11**) (0.65 g, 23% yield) as a low melting solid; $\nu_{max.}$ 3 250 cm^{-1}; $\delta_H(CD_3OD)$ 0.9 (3 H, t), 1.3 (26 H, m), 1.6—1.8 (2 H, m), 1.9—2.4 (2 H, m), 3.55 (2 H, d, *J* 6 Hz), and 4.75 (2 H, br s, OH and NH); $\delta_C([^2H_5]$pyridine) 61.7, 36.5, 34.9, 32.2, 30.0, 29.6, 29.4, 28.6, 22.9, and 14.3; *m/z* 283 (M^+, 8%), 253 (23), 252 (100), and 135 (10) (Found: C, 76.2; H, 13.1; N, 4.9. $C_{18}H_{37}NO$ requires C, 76.26; H, 13.16; N, 4.94%).

erythro-2-*Acetamido*-1,3-*diacetoxyoctadecane* (erythro-*Sphinganine Triacetate*) (**1**).—The dihydro-oxazole (**10**) (1.3 g, 3 mmol) was dissolved in MeOH (60 ml) and the solution was then removed under reduced pressure and the residue was directly acetylated with pyridine (3 ml) and Ac_2O (0.5 ml). After 18 h, the solvents were stripped off under reduced pressure and the residue was chromatographed through silica gel, with

cyclohexane–AcOEt as eluant, to give the triacetate (**1**) (0.9 g, 70%) as a white solid, m.p. 89—91 °C (lit.,[6d] 90—92 °C); $\nu_{max.}$ 3 300, 1 730, 1 650, and 1 550 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (3 H, t), 1.26 (26 H, m), 1.62 (2 H, m), 2.04 (3 H, s), 2.09 (6 H, s), 4.12 (2 H, m, CH_2O), 4.28 (1 H, m, CHN), 4.96 (1 H, m, CHO), and 6.02 (1 H, d, *J* 9 Hz, NH); after irradiation at δ_H 4.28, the multiplets at δ_H 4.12 and 4.96 collapsed: the latter one appeared as a triplet (*J* 6.5 Hz) and a coupling constant *J* 5.5 Hz was deleted. In contrast, after irradiation at δ_H 4.96, only the multiplet at δ_H 4.28 collapsed. $\delta_C([^2H_6]acetone)$ 73.6, 63.4, 51.0, 31.7, 29.8, 29.7, 29.5, 29.4, 28.9, 28.5, 25.9, 23.3, 22.9, 20.9, 20.7, and 14.3; *m/z*, 427 (M^+, 1%), 308 (9), 295 (15), 188 (8), 145 (61), 85 (90), and 84 (100).

threo-2-*Amino*-3-*iodo-octadecan*-1-*ol Hydrochloride* (**13**).—The oxazole (**8**) (5.4 g, 10 mmol) was treated with 2M-HCl (10 ml) at room temperature. The solution was then evaporated under reduced pressure and the residue was washed with AcOEt to remove trichloroacetic acid, and the salt (**13**) was obtained in quantitative yield as a low melting solid; $\nu_{max.}$ 3 340 cm^{-1}; δ_H ($[^2H_6]$benzene) 0.9 (3 H, t), 1.3 (26 H, m), 1.6—1.8 (2 H, m), 3.5—3.65 (1 H, m), 3.7—4.5 (3 H, m), and 5.9 (4 H, br s, OH, and NH_3^+); $\delta_C(CD_3OD)$ 62.4, 59.5, 37.5, 33.7, 33.0, 30.7, 30.4, 29.5, 23.7, and 14.4.

cis-2-*Hydroxymethyl*-3-*pentadecylaziridine* (**11**).—To a solution of the salt (**13**) (1.1 g, 4 mmol) in MeOH (15 ml) was added Amberlyst A 26 (CO_3^{2-} form) (4 g: ~3.8 mequiv. g^{-1}) at room temperature, and the mixture was stirred for 1 h. The resin was then filtered off, and the solvent was evaporated off under reduced pressure to give the aziridine (**11**) in quantitative yield.

threo-2-*Acetamido*-1,3-*diacetoxyoctadecane* (threo-*Sphinganine Triacetate*) (**2**).—A solution of the aziridine (**11**) (0.85 g, 3 mmol) in MeOH was treated with 2M-HCl (1.5 ml) and the solvent was evaporated off under reduced pressure. The hydrochloride (**14**) was then dissolved in benzene (10 ml), Amberlyst A 26 (AcO^- form) (3 g; ~3.8 mequiv. g^{-1}) was added, and the suspension was refluxed for 12 h. The resin was then filtered off, and the solvent was evaporated off under reduced pressure to give a regioisomeric mixture of the amides (**15**) and (**16**) ($\nu_{max.}$ 3 300, 1 650, and 1 510 cm^{-1}) which were directly acetylated with pyridine (5 ml) and acetic anhydride (1 ml). After 18 h at room temperature, the solvents were removed under reduced pressure and the residue was chromatographed through silica gel with cyclohexane–AcOEt (8:2) as eluant, to give *triacetate* (**17**) (0.23 g, 18%) as a low melting solid; $\nu_{max.}$ 3 300, 1 730, 1 650, and 1 550 cm^{-1}; $\delta_H(CDCl_3)$ 0.89 (3 H, t), 1.29 (28 H, m), 2.04 (3 H, s), 2.07 (3 H, s), 2.14 (3 H, s), 4.11 and 4.28 (2 H, *AB*X, CH_2O), 4.30 (1 H, m, CHN), 5.27 (1 H, m, CHO), and 5.51 (1 H, d, *J* 9 Hz, NH); after irradiation at δ_H 5.27, the *AB*X system at δ_H 4.11 and 4.28 collapsed to an AB quartet (*J* 12 Hz); $\delta_C([^2H_6]acetone)$ 73.4, 64.2, 49.5, 32.6, 31.9, 30.9, 30.4, 30.1, 29.9, 28.9, 26.6, 25.9, 23.3, 22.9, 20.9, 20.8, and 14.5; *m/z*, 427 (M^+, 2), 284 (25), 283 (100), 242 (16), 241 (83), and 97 (14) (Found: C, 67.3; H, 10.7; N, 3.15. $C_{24}H_{45}NO_5$ requires C, 67.41; H, 10.61; N, 3.28%).

Further elution with cyclohexane–AcOEt (8:2) as eluant afforded the regioisomer (**2**) (0.72 g, 56%) as a white solid, m.p. 65—66 °C (lit.,[6d] 65—66 °C); $\nu_{max.}$ 3 300, 1 730, 1 650, and 1 550 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (3 H, t), 1.26 (26 H, m) 1.58 (2 H, m), 2.05 (3 H, s), 2.08 (3 H, s), 2.10 (3 H, s), 4.08 (2 H, m, CH_2O), 4.45 (1 H, m, CHN), 5.13 (1 H, m, CHO), and 5.58 (1 H, d, *J* 9 Hz, NH); $\delta_C([^2H_6]acetone)$ 72.9, 63.9, 50.3, 32.6, 31.9, 30.9, 30.4, 30.1, 29.9, 28.9, 26.6, 25.9, 23.3, 22.9, 20.9, 20.8, and 14.5; *m/z* 427 (M^+, 1), 308 (9), 295 (15), 188 (8), 145 (61), 85 (90), and 84 (100).

threo-2-*Acetamido*-1,3-*diacetoxyoctadecane* (threo-*Sphinganine Triacetate*) (**2**).—To a solution of the salt (**13**) (3.6 g, 8 mmol) in dry benzene (20 ml) was added Amberlyst A 26 (AcO^- form) (8 g; ~3.8 mequiv. g^{-1}) and the suspension was refluxed for 12 h. The resin was then filtered off, and the solvent was evaporated off under reduced pressure to give the amides (**15**) and (**16**), as a regioisomeric mixture, which were directly acetylated with pyridine (5 ml) and acetic anhydride (1 ml). After 18 h at room temperature, the solvent was removed under reduced pressure and the residue was chromatographed through silica gel with cyclohexane–AcOEt (8:2) as eluant, to give triacetate (**17**) (0.68 g, 20%) as a low melting solid. Further elution afforded the title compound (**2**) (2.0 g, 58%) as a white solid.

Octadec-1-*en*-3-*ol* (**18**).—The product (**18**) was obtained as described in ref. 7, $\nu_{max.}$ 3 340 and 920 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (3 H, t), 1.3 (26 H, m), 1.6—1.8 (2 H, m), 2.3 (1 H, br s, OH), 3.9—4.3 (1 H, m), and 5.0—6.2 (3 H, m); $\delta_C(CDCl_3)$ 141.4, 114.4, 73.3, 37.1, 31.9, 29.7, 29.4, 28.7, 25.4, 22.7, and 14.1.

3-*Trichloroacetimidoyloxyoctadec*-1-*ene* (**19**).—To a solution of the alcohol (**18**) (4.0 g, 15 mmol) in dry THF (20 ml) under an inert atmosphere was added Bu^nLi (1.8M in hexane; 1.4 ml, 2.5 mmol). After 20 min, the mixture was cooled to 0 °C and a solution of trichloroacetonitrile (2.3 g, 16 mmol) in dry THF (5 ml) was added dropwise, and the mixture was then stirred for 1 h. Then MeOH (1 ml) was added and the solvent was removed under reduced pressure. The residue was chromatographed through silica gel with cyclohexane–AcOEt (98:2) as eluant to give the title imidate (**19**) (5.5 g, 90%) as an oil; $\nu_{max.}$ 3 350 and 1 660 cm^{-1}; $\delta_H(CDCl_3)$ 0.85 (3 H, t), 1.25 (26 H, m), 1.6—1.9 (2 H, m), 5.0—6.2 (4 H, m), and 8.3 (1 H, br s, NH); $\delta_C(CDCl_3)$ 135.8, 116.6, 79.5, 32.0, 29.7, 29.4, 25.0, 22.7, and 14.1.

cis- and trans-4-*Iodomethyl*-5-*pentadecyl*-2-*trichloromethyl*-4,5-*dihydro-oxazole* (**20a** *and* **b**).—To a solution of the imidate (**19**) (4.1 g, 10 mmol) in $CHCl_3$ (150 ml) was added NIS (2.5 g, 11 mmol). After being stirred for 12 h, the solution was washed with saturated aqueous $Na_2S_2O_3$ and the organic phase was evaporated under reduced pressure. The residue was chromatographed through silica gel with cyclohexane–AcOEt (98:2) as eluant to give the title oxazole as a *cis*:*trans* mixture (**20a**) and (**20b**) in the ratio 20:80 as an oil (4.8 g, 90%); $\nu_{max.}$ 1 650 cm^{-1}; $\delta_H(CDCl_3)$ 0.9 (3 H, t), 1.3 (26 H, m), 1.6—1.8 (2 H, m), 3.4 (2 H, d, *J* 5 Hz), 3.8—4.3 (1 H, m), and 4.4—4.9 (1 H, q).

cis-*Isomer* (**20a**): $\delta_C(CDCl_3)$ 87.1, 69.7, 34.9, 31.7, 29.7, 29.4, 27.5, 27.0, 26.0, 24.3, 22.7, 14.2, and −0.07. trans-*Isomer* (**20b**): $\delta_C(CDCl_3)$ 89.5, 71.4, 34.9, 31.7, 29.7, 29.4, 27.5, 27.0, 26.0, 24.3, 22.7, 14.2, and 8.6 (Found: C, 36.2; H, 5.4; N, 2.0. $C_{20}H_{35}Cl_3INO$ requires C, 36.09; H, 5.30; N, 2.10%).

erythro- and threo-2-*Amino*-1-*iodo-octadecan*-3-*ol Hydrochloride* (**21a** *and* **b**).—The diastereoisomeric mixture of dihydro-oxazoles (**20a** and **b**) (4.3 g, 8 mmol) was dissolved in acetone (50 ml) and the solution was treated with 2M-HCl (10 ml) for 1 h at room temperature. The solvent was then stripped off under reduced pressure and the residue was washed with AcOEt to remove trichloroacetic acid; the diastereoisomeric mixture of the salts (**21a** and **b**) was obtained in quantitative yield as a low melting solid; $\nu_{max.}$ 3 340 cm^{-1}; $\delta_C(CD_3OD)$ 0.9 (3 H, t), 1.3 (26 H, m), 1.6—1.8 (2 H, m), 3.3 (2 H, d), and 4.5—5.0 (2 H, m); $\delta_C(CD_3OD)$ 71.4, 57.3, 34.2, 32.8, 30.5, 30.2, 26.0, 23.5, 14.5, 2.8, and 0.1.

Alternative Preparation of threo-2-*Acetamido*-1,3-*diacetoxyoctadecane* (threo-*Sphinganine Triacetate*) (**2**) *and* erythro-2-*Acetamido*-1,3-*diacetoxyoctadecane* (erythro-*Sphinganine Triacetate*) (**1**).—A diastereoisomeric mixture of salts (**21a** and **b**) (3.6 g, 8 mmol) was dissolved in benzene (20 ml) and Amberlyst

A 26 (AcO^- form) (8 g, ~3.8 mequiv. g^{-1}) was added. The suspension was refluxed for 6 h, then the resin was filtered off and the solvent was removed under reduced pressure, to give a diastereoisomeric mixture of the amides (**22a** and **b**) ($\nu_{max.}$ 3 300, 1 650, and 1 550 cm^{-1}) which was directly acetylated with acetic anhydride (1 ml) in pyridine (3 ml). After 18 h at room temperature, the solvents were evaporated off under reduced pressure and the residue was chromatographed through silica gel with cyclohexane–AcOEt (1:1) as eluant, to give compound (**2**) (1.8 g, 52%) as a white solid, m.p. 65—66 °C (lit.,[6d] 65—66 °C).

Further elution gave compound (**1**) as a white solid (0.45 g, 13%), m.p. 89—91 °C (lit.,[6d] 90—92 °C).

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