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Total Synthesis of Symbioramide: a Flexible Approach for the Efficient Preparation of Structural Isomers

Sébastien Prévost,[a,b] Tahar Ayad,[a,b] Phannarath Phansavath,[a,b,*] and Virginie Ratovelomanana-Vidal[a,b,*]

[a] ENSCP Chimie ParisTech, Laboratoire Charles Friedel (LCF), 75005 Paris, France
[b] CNRS, UMR 7223, 75005 Paris, France
Fax: (+33)-1-4407-1062; e-mail: phannarath-phansavath@chimie-paristech.fr or virginie-vidal@chimie-paristech.fr

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Abstract: A concise, enantioselective total synthesis of symbioramide, starting from simple achiral compounds and racemic α-amino-β-keto ester derivatives is reported. This highly flexible strategy allowed the efficient preparation of seven structural isomers of the natural product as well. The synthesis relies on a convergent route that involves the efficient stereoselective reduction of a α-keto-β-yne ester, and the dynamic kinetic resolution of an α-amino-β-keto ester through ruthenium-mediated asymmetric hydrogenation.

Keywords: asymmetric catalysis; dynamic kinetic resolution; hydrogenation; ruthenium; total synthesis

Introduction

Symbioramide (**1**) is a naturally occuring bioactive ceramide that has been isolated by Kobayashi et al.[1] from the laboratory-cultured dinoflagellate *Symbiodinium* sp., obtained from the inside of gill cells of the Okinawan bivalve *Fragum* sp. This sphingosine derivative was the first example of a sarcoplasmic reticulum Ca^{2+}-ATPase activator from a marine source. In addition, symbioramide has been found to exhibit antileukemic activity against L1210 murine leukemia cells *in vitro* with an IC_{50} value of 9.5 $\mu g\,mL^{-1}$. The structure of symbioramide was initially proposed as (2*S*,3*R*,3′*E*)-*N*-(2′-hydroxy-3′-octadecenoyl)dihydrosphingosine, composed of D-*erythro*-dihydrosphingosine as the amino part and (2*R*,3*E*)-2-hydroxy-3-octadecenoic acid as the acid part, with unknown absolute configuration at C-2′.

Due to its significant biological properties as well as its interesting structural features, several syntheses of symbioramide have been reported. The first total synthesis of **1**, reported by Nakagawa, Hino et al.[2] relied on the use of L-ascorbic acid and L-serine as chiral synthons for the preparation of, respectively, the unusual fatty acid subunit and the D-*erythro*-dihydrosphingosine part. Moreover, the synthesis of both enantiomers of methyl (*E*)-2-hydroxy-3-octodecenoate allowed the authors to unambiguously establish the absolute stereochemistry at the C-2′ position to be *R*. A synthesis of symbioramide based on Sharpless asymmetric epoxidation for the preparation of the (2*R*,3*E*)-2-hydroxy-3-octadecenoic acid fragment was later reported by Mori et al.,[3] who also relied on L-serine to attain the D-*erythro*-dihydrosphingosine part by using a known route. Azuma, Ogino et al.[4] described the total syntheses of symbioramide and derivatives starting from L-serine for the preparation of both the fatty acid fragment and the dihydrosphingosine subunit. However, a major drawback of this approach lies in the construction of the (*E*)-olefin of the acid part, which was obtained through photoisomerization of the (*Z*)-isomer using diphenyl disulfide, as a 76:24 mixture of *E*:*Z* olefins which had to be separated by column chromatography followed by recrystallization. A chemo-enzymatic total synthesis of symbioramide was later reported by the group of Sugai in 2005.[5] This approach relied on a lipase-catalyzed coupling between (±)-dihydrosphingosine and an (*R*)-β,γ-unsaturated α-hydroxy ester, both of which were derived from a common intermediate, methyl (±)-*trans*-2,3-epoxyoctadecanoate. Although concise, this route suffers from the inherent drawback associated with enzymatic methods, which give at the most 50% yield of the desired enantiomerically enriched compound. Moreover, the direct enzyme-mediated coupling reaction proceeded in a non-enantioselective

manner, delivering both symbioramide and the unnatural diastereomer, which were separated on column chromatography. More recently, Posner et al. achieved a formal synthesis of symbioramide by using an elegant asymmetric organocatalytic approach to α-hydroxy (*E*)-β,γ-unsaturated esters.[6]

In order to complement the reported total syntheses of **1** which generally involved enzymatic routes or chiral pool-based approaches, we were interested in designing an efficient catalytic approach to the natural product.

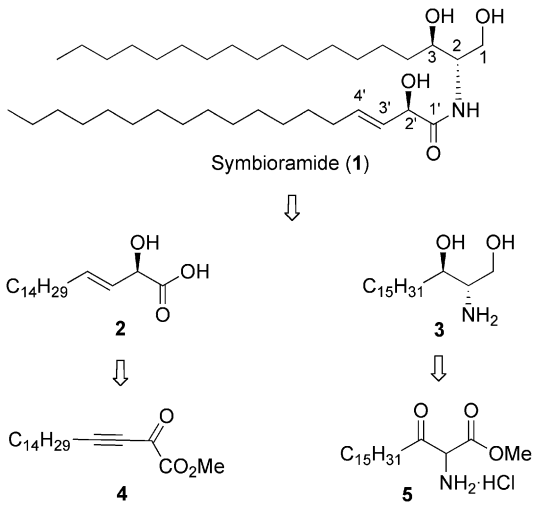
Thus, as an extension of our work on dynamic kinetic resolution (DKR) of α-amino-β-keto ester hydrochlorides through ruthenium-catalyzed asymmetric hydrogenation,[7] and in connection with our ongoing projects involving the synthesis of biologically relevant natural products *via* transition metal-promoted reactions,[8] we report herein an application of this methodology to the total synthesis of symbioramide.

From a retrosynthetic point of view, symbioramide can be disconnected at the amide bond into (2*R*,3*E*)-2-hydroxy-3-octadecenoic acid **2** and D-*erythro*-dihydrosphingosine **3** (Scheme 1).

Subunit **2** would result from stereoselective reduction of the ketone function of an α-keto-β,γ-unsaturated ester **4** through asymmetric transfer hydrogenation, followed by stereoselective reduction of the alkyne into the corresponding (*E*)-alkene. On the other hand, D-*erythro*-dihydrosphingosine **3** would be obtained *via* ruthenium-catalyzed asymmetric hydrogenation[9] of the racemic α-amino-β-keto ester hydrochloride **5** through DKR.[10]

Interestingly, this approach opens an easy access to all sixteen diastereomers of symbioramide. Indeed, on the one hand, enantioselective reduction of ketone **4** would deliver both enantiomers of the corresponding alcohol, whereas stereoselective reduction of the alkyne function would furnish both the corresponding (*Z*) and (*E*)-alkenes **2**. On the other hand, ruthenium-mediated asymmetric hydrogenation of **5** or of the parent compound, an α-amido-β-keto ester, would readily afford respectively the *anti*[7,11] or *syn*[12] isomers of **3**. Coupling of these various isomers of subunits **2** and **3** would then produce all sixteen stereoisomers of symbioramide.

Following this strategy, we report herein the concise stereodivergent synthesis of eight stereoisomers of symbioramide, including the natural compound, starting from prochiral **4** and racemic **5**.

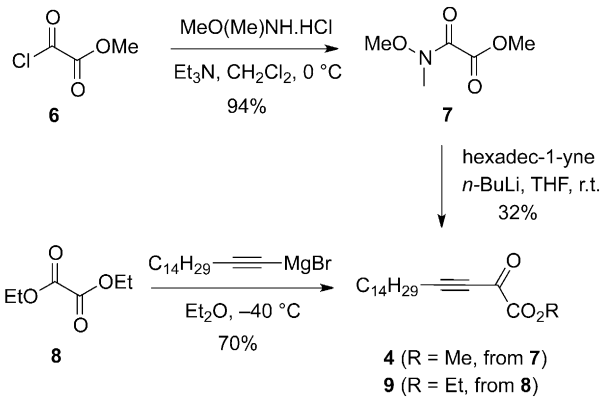


Scheme 1. Retrosynthetic analysis of symbioramide **1**.

Results and Discussion

The synthesis of methyl oxooctadecanoate **4** relied initially on conversion of monomethyl oxalyl chloride **6** into Weinreb amide **7**,[13] followed by addition of hexadec-1-yne which furnished the target compound[14] in 30% overall yield (Scheme 2). However, the parent compound ethyl oxooctadecanoate **9** was more efficiently prepared in 70% yield by reaction of *n*-hexadecylmagnesium bromide with diethyl oxalate **8**.[15]

To the best of our knowledge, the stereoselective reduction of α-keto-β,γ-acetylenic esters has not been reported so far. However, since transition metal-catalyzed asymmetric transfer hydrogenation (ATH)[16] of either α,β-acetylenic ketones or α-keto esters is an efficient method for the preparation of, respectively, enantiomerically enriched propargylic alcohols or α-hydroxy esters, we logically decided to investigate the ATH of α-keto-β,γ-acetylenic esters **4** and **9** in order to synthesize the corresponding α-hydroxy-β,γ-acetylenic esters. Nevertheless, since our preliminary efforts to optimize this reaction with either the Noyori catalyst [(*S*,*S*)-RuCl(*p*-cymene)(Ts-DPEN)][17] or other ruthenium, iridium and rhodium complexes were unsuccessful,[18] we chose to use stoichiometric methods for the preparation of the desired enantio-

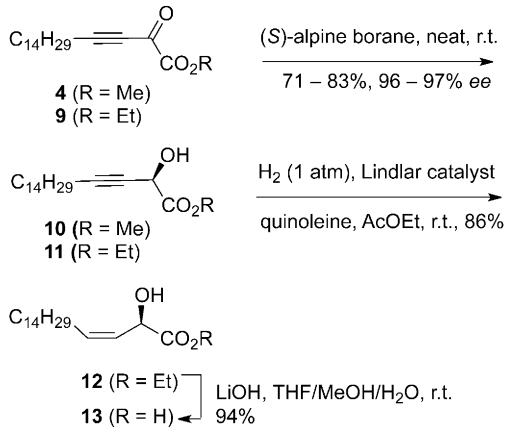


Scheme 2. Preparation of α-keto-β,γ-acetylenic esters **4** and **9**.

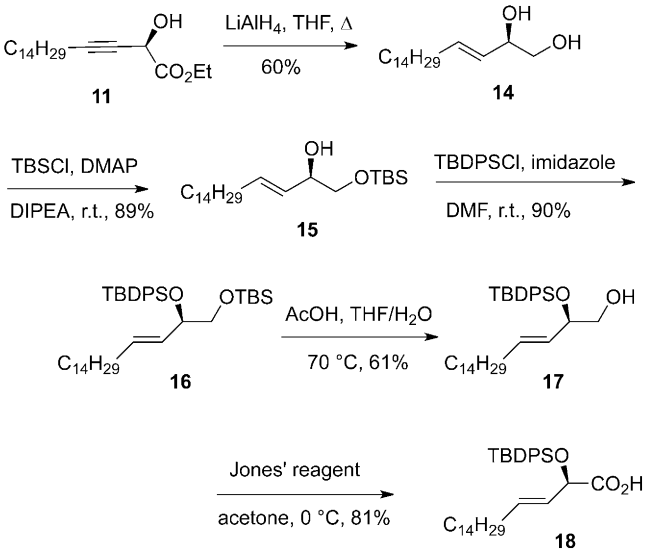
merically enriched alcohols. Thus, methyl oxooctadecanoate **4** was treated with the Corey–Bakshi–Shibata oxazaborolidine[19] in the presence of $BH_3{\cdot}Me_2S$. The reaction afforded **10** in a good 76% yield but with a moderate 34% *ee*. The stereoselective reduction of **4** and of the parent compound, ethyl oxooctadecanoate **9**, was nevertheless successfully accomplished by using (*S*)-alpine borane[20] which furnished, respectively, the enantiomerically enriched alcohols **10** and **11** in good yields (71–83%) and excellent enantioselectivities (96–97% *ee*)[21] after careful optimization of the reaction conditions (Scheme 3).

Subsequent hydrogenation of **11** using Lindlar catalyst, followed by hydrolysis of the ester function then delivered the expected (*Z*)-allylic alcohol **13** in 81% yield.

For the synthesis of the related (*E*)-isomer **18** (Scheme 4), conversion of propargylic alcohol **11** into



Scheme 3. Preparation of the (*Z*)-fatty acid subunit **13**.



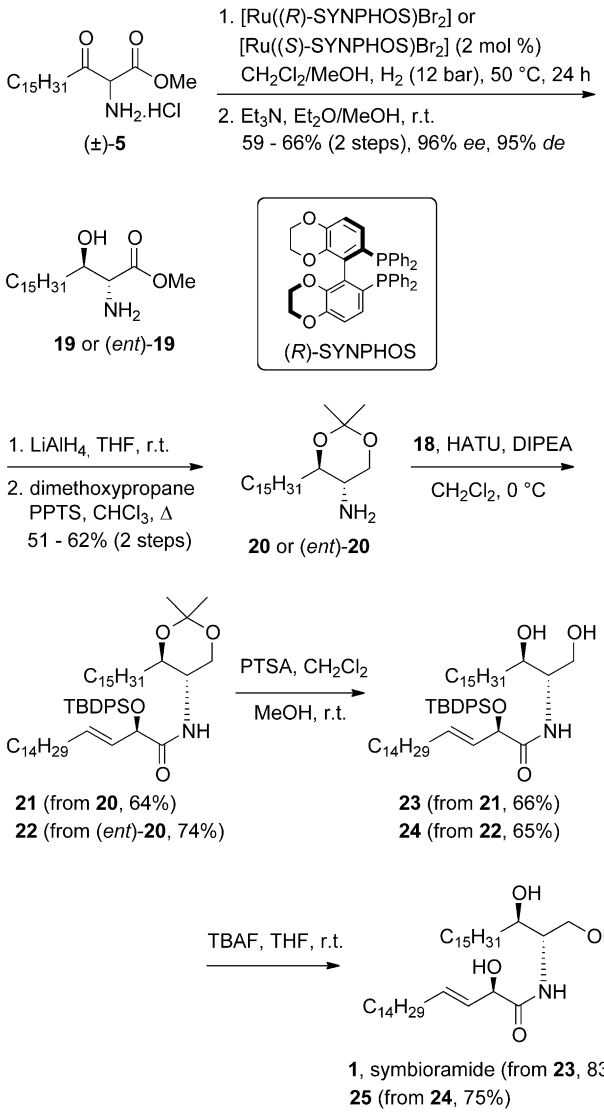
Scheme 4. Preparation of the (*E*)-fatty acid subunit **18**.

the corresponding (*E*)-allylic alcohol was first attempted using Red-Al. With this reagent, however, only reduction of the ester function occurred, and no trace of alkene was observed. A hydrosilylation/protodesilylation sequence using $(EtO)_3SiH$ and the $[Ru(NCMe)_3Cp^*]PF_6$ complex[22] was next applied. Unfortunately, despite considerable experimentation, the desired (*E*)-allylic alcohol could not be obtained in acceptable yields by using this approach. On the other hand, the required (*E*)-alkene **18** was synthesized from **11** using a five-step sequence as depicted below (Scheme 4).

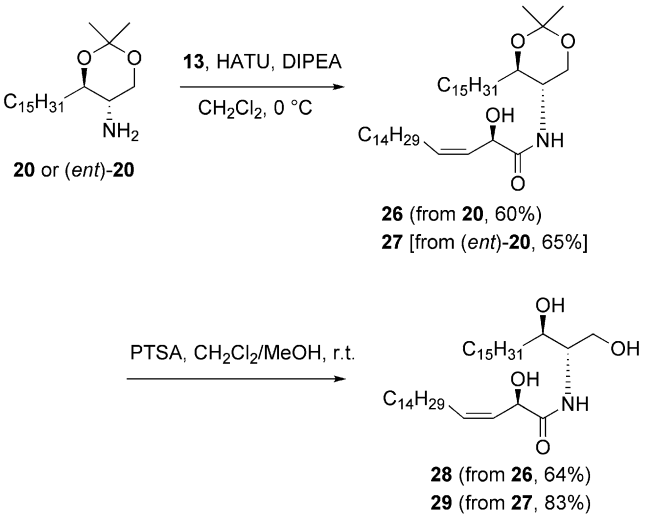
Treatment of **11** with $LiAlH_4$ in refluxing THF allowed the formation of diol **14** in 60% yield. After a protection/deprotection sequence of the diol moiety, the primary alcohol of **17** was finally oxidized with the Jones reagent to the corresponding carboxylic acid **18**, ready for the peptide coupling reaction with the D-*erythro*-dihydrosphingosine part.

Having secured the preparation of the hydroxyoctadecanoic fragments, we then turned to the synthesis of the dihydrosphingosine counterparts starting from racemic α-amino-β-keto ester derivatives. The hydrogenation reaction of compound **5**[10c] was first attempted using an iridium complex bearing as a ligand the atropisomeric diphosphine SYNPHOS[23] developed in our group (Scheme 5).

Thus the reaction was carried out with 1 mol% of the $[\{Ir((S)\text{-SYNPHOS})H\}_2(\mu\text{-}Cl)_3]Cl$ complex,[24] under 75 bar of hydrogen in a CH_2Cl_2/MeOH mixture at 50 °C for 48 h. Under these conditions, however, a low conversion of 20% was observed. Ruthenium-mediated asymmetric hydrogenation of **5** was then attempted using 2 mol% of {RuCl[(*S*)-SYNPHOS]-(*p*-cymene)}Cl[25] complex in CH_2Cl_2/MeOH at 50 °C under 12 bar of hydrogen. Nevertheless, after 24 h of reaction, no trace of the expected alcohol was observed. The reduction was also carried out using the convenient procedure developed in our laboratories for the *in situ* preparation of chiral ruthenium-diphosphine complexes starting directly from $RuCl_3$.[26] However, hydrogenation of **5** using 2 mol% of $RuCl_3$ associated to (*R*)-SYNPHOS as a ligand showed no conversion at all. Finally, the asymmetric hydrogenation of α-amino-β-keto ester hydrochloride **5** was performed using ruthenium(II) complexes prepared *in situ* from [Ru(1,5-cyclooctadiene)(2-methylallyl)$_2$].[27] The reaction was conducted in CH_2Cl_2/MeOH at 50 °C under 12 bar of hydrogen in the presence of 2 mol% of either {Ru[(*R*)-SYNPHOS]Br_2} or {Ru[(*S*)-SYNPHOS]Br_2} complex,[7a,b] and afforded respectively the *anti* amino alcohols **19** and (*ent*)-**19** in high enantio- and diastereoselectivities after treatment of the hydrogenated products with triethylamine in Et_2O/MeOH. These compounds were reduced to the corresponding diols using $LiAlH_4$ and protected as their acetonides **20** and (*ent*)-**20** by treatment with



Scheme 5. Total synthesis of symbioramide (**1**) and of its structural isomer **25**.



Scheme 6. Synthesis of symbioramide structural isomers **28** and **29**.

dimethoxypropane/PPTS in refluxing chloroform. Coupling of these compounds with (*E*)-carboxylic acid **18** proceeded cleanly using HATU/DIPEA in dichloromethane and the expected peptides **21** and **22** were obtained in 64–74% yields. Subsequent global deprotection of the hydroxy functions with successively PTSA and TBAF then delivered symbioramide **1** and its structural isomer **25**, respectively. The spectral data of synthetic symbioramide were found to be in agreement with those reported for the natural product {$[\alpha]_D^{20}$: +4.7 (*c* 0.29, $CHCl_3$), lit.:[1a] $[\alpha]_D^{22}$: +5.8 (*c* 1, $CHCl_3$)}.

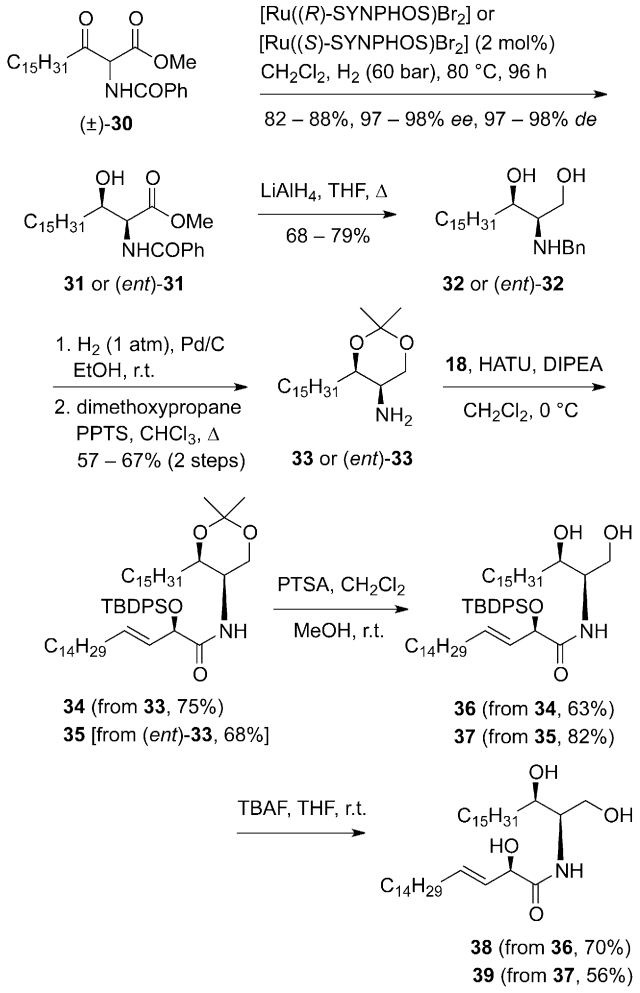
In order to synthesize the related (*Z*)-isomers **28** and **29** of symbioramide, compounds **20** and (*ent*)-**20** were subjected to peptide coupling reaction with (2*R*,3*Z*)-2-hydroxy-3-octadecenoic acid **13** under the conditions mentioned above (Scheme 6). Peptides **26** and **27** were thus obtained in 60–65% yield, allowing after acetonide removal, the enantioselective synthesis of two other symbioramide isomers **28** and **29**.

Preparation of the *syn*-1,2-amino alcohol isomers of symbioramide relied on the ruthenium-catalyzed asymmetric hydrogenation of α-amido-β-keto ester **30**.[7a,b] The reaction was conducted in CH_2Cl_2 at 80 °C under 60 bar of hydrogen in the presence of 2 mol% of either {Ru[(*R*)-SYNPHOS]Br_2} or {Ru[(*S*)-SYNPHOS]Br_2} complexes, and afforded respectively the *syn*-amino alcohols **31** and (*ent*)-**31** in high enantio- and diastereoselectivities up to 98% *ee* and 98% *de* (Scheme 7). Treatment of these compounds with excess $LiAlH_4$ in refluxing THF provided the corresponding benzylaminodiols and subsequent debenzylation (H_2, Pd/C) followed by protection of the 1,3-diol moiety delivered acetonides **33** and (*ent*)-**33** in good 57–67% overall yields. Coupling of these compounds with (*E*)-carboxylic acid **18** and subsequent acetonide removal then yielded **36** and **37**.

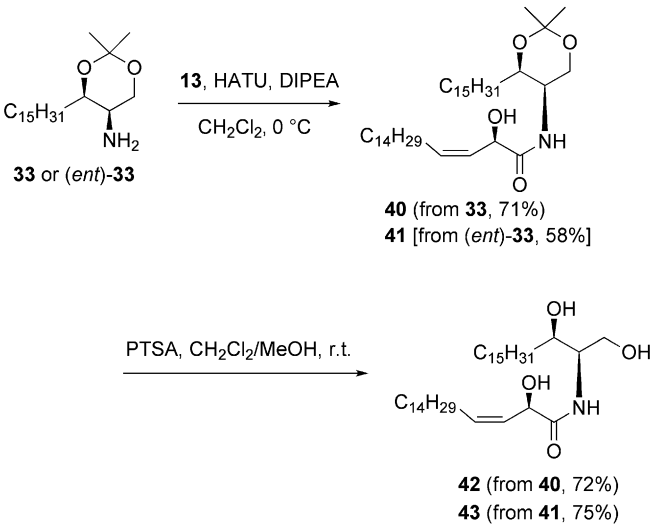
Finally, deprotection of the remaining hydroxy function with TBAF delivered two novel structural isomers **38** and **39** of symbioramide.

The related (*Z*)-isomers **42** and **43** were prepared as well from compounds **33** and (*ent*)-**33** according to the two-step sequence employed for the synthesis of **28** and **29** (Scheme 8).

Thus, coupling of **33** and (*ent*)-**33** with the fatty acid subunit **13** in the presence of HATU/DIPEA provided **40** and **41**, which were subsequently subjected to PTSA in CH_2Cl_2/MeOH to afford structural isomers **42** and **43** of symbioramide in good overall yields.



Scheme 7. Synthesis of symbioramide structural isomers **38** and **39**.



Scheme 8. Synthesis of symbioramide structural isomers **42** and **43**.

Conclusions

In summary, a short and efficient synthesis of symbioramide **1** was achieved starting from readily accessible racemic α-amino-β-keto ester **5** and α-keto-β,γ-unsaturated ester **4**. Application of the ruthenium-catalyzed asymmetric hydrogenation reaction to racemic α-amino-β-keto ester derivatives **5** and **30** allowed the preparation of the corresponding *anti*- and *syn*-amino alcohols in high enantio- and diastereoselectivities through a dynamic kinetic resolution process. Furthermore, an efficient preparation of both (*E*)- and (*Z*)-isomers of the α-hydroxy β,γ-unsaturated fatty acid part has been achieved by stereoselective reduction of the ketone and alkyne functions of α-keto-β,γ-unsaturated ester **9**. This flexible strategy allowed the short synthesis of seven structural isomers of symbioramide, namely compounds **25**, **28**/**29**, **38**/**39**, and **42**/**43** which were efficiently obtained in high enantio- and diastereoselectivities.

Experimental Section

General Remarks

All air- and/or water-sensitive reactions were carried out under an argon atmosphere. Tetrahydrofuran and diethyl ether were distilled from sodium-benzophenone. Dichloromethane was distilled from calcium hydride. Reactions were monitored by thin layer chromatography carried out on precoated silica gel plates (E. Merck ref. 5554 60 F254) and revealed with either a ultra-violet lamp ($\lambda = 254$ nm) or a potassium permanganate solution. The nuclear magnetic resonance spectra were recorded on a Bruker AC 300 or Avance 400 instrument at 300 or 400 MHz, respectively, for ^{1}H and 75 or 100 MHz, respectively, for ^{13}C. The chemical shifts are expressed in parts per million (ppm) referenced to residual chloroform (7.26 ppm for ^{1}H and 77.1 ppm for ^{13}C). Data are reported as follows: chemical shifts (δ), multiplicity (recorded as s, singlet; d, doublet; t, triplet; q, quadruplet; sept, septuplet; m, multiplet; and br, broad), integration and coupling constants. Melting points (mp) were determined on a Büchi apparatus and are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. High resolution mass spectrometric (HR-MS) analyses were measured on LTQ-Orbitrap (Thermo Fisher Scientific) at Pierre et Marie Curie University.

General Procedure for the Dynamic Kinetic Resolution of α-Amino-β-keto Ester Derivatives through Asymmetric Hydrogenation

(*R*)- or (*S*)-SYNPHOS (28.1 mg, 0.044 mmol) and [Ru(1,5-cyclooctadiene)(η^3-$(CH_2)_2CHCH_3)_2$] (12.8 mg, 0.04 mmol) were placed in a round-bottom tube, degassed by three vacuum/argon cycles at room temperature, and dissolved in degassed acetone (1 mL). To this suspension was added dropwise at room temperature, methanolic hydrobromic acid (0.088 mmol, 564 μL of a 0.156 N solution) and the mix-

ture was stirred at room temperature for 30 min. The suspension immediately turned yellow, and then an orange precipitate appeared. The solvent was thoroughly evaporated under vacuum to afford the ruthenium complex as an orange-brown solid. A solution of α-amino-β-keto ester (2 mmol) in either CH_2Cl_2/MeOH (4 mL) or CH_2Cl_2 (4 mL) was added to the ruthenium complex and the resulting mixture was placed under the desired hydrogen pressure and temperature for either 24 h or 96 h. After removal of the solvent, the crude product was either directly used for the next step used or purified by flash chromatography on silica gel.

Monomethyloxalic Acid *N*-Methoxy-*N*-methylamide (7)[13]

To a solution of *N,O*-dimethylhydroxylamine hydrochloride (5.29 g, 54.2 mmol) and monomethyl oxalyl chloride (5.0 mL, 54.2 mmol) in CH_2Cl_2 (350 mL) was added triethylamine (15.2 mL, 108.5 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C, and concentrated after addition of MeOH (7 mL). THF (150 mL) was then added, the mixture was filtered, washed with THF and concentrated under vacuum. Purification of the residue by distillation (kugelrohr, bp 114–120 °C/2–3 torr), afforded **7** as a colorless oil; yield: 7.50 g (94%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.84$ (s, 3H), 3.72 (s, 3H), 3.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 162.8$, 161.8, 62.3, 52.6, 31.4.

Methyl 2-Oxooctadec-3-ynoate (4)

To a solution of 1-hexadecyne (2.37 mL, 8.5 mmol) in THF (15 mL) was added *n*-BuLi (2.1 M in hexane, 3.95 mL, 8.3 mmol) at −30 °C. The mixture was stirred for 2 h at room temperature and was added dropwise to a solution of **7** (1.0 g, 6.80 mmol) in THF (10 mL) at −78 °C. The temperature was slowly raised to room temperature and the mixture was stirred for 15 h. The solution was filtered on a silica pad and the solvent was removed under vacuum. Purification of the residue by flash chromatography (pentane/diisopropyl ether: 96/4 to 9/1) afforded **4** as a pale yellow oil; yield: 662 mg (32%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 3.91$ (s, 3H), 2.47 (t, 2H, $J = 7.1$ Hz), 1.68–1.55 (m, 2H), 1.48–1.36 (m, 2H), 1.24 (br s, 20H), 0.88 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 169.3$, 159.8, 103.0, 79.8, 53.6, 32.0, 29.8, 29.7, 29.5, 29.1, 29.0, 27.5, 22.8, 19.6, 14.2.

Ethyl 2-Oxooctadec-3-ynoate (9)

To a solution of 1-hexadecyne (4.6 mL, 16.5 mmol) in Et_2O (50 mL) was added ethyl magnesium bromide (0.78 M in Et_2O, 23.2 mL, 18.1 mmol). The mixture was stirred for 6 h under reflux, then added dropwise to a solution of diethyl oxalate (2.5 mL, 18.1 mmol) in Et_2O (20 mL) at −30 °C. The mixture was stirred for 1.5 h at this temperature and saturated NH_4Cl was added. The aqueous layer was extracted with $(i\text{-Pr})_2O$, the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (cyclohexane/diisopropyl ether: 95/5) afforded **9** as a pale yellow oil; yield: 3.72 g (70%). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta =$ 4.35 (q, 2H, $J = 7.1$ Hz), 2.47 (t, 2H, $J = 7.1$ Hz), 1.70–1.55 (m, 2H), 1.49–1.34 (m, 2H), 1.38 (t, 3H, $J = 7.1$ Hz), 1.25 (br s, 20H), 0.87 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 169.9$, 159.5, 102.8, 79.9, 63.3, 32.1, 29.8, 29.7, 29.5, 29.1, 29.0, 27.5, 22.8, 19.6, 14.2, 14.1; HR-MS (ESI): $m/z = 345.2401$, calcd. for $C_{20}H_{34}O_3Na$ $[M+Na]^+$: 345.2400.

(2*R*)-Methyl 2-Hydroxyoctadec-3-ynoate [(*R*)-10] and (2*S*) Methyl 2-Hydroxyoctadec-3-ynoate [(*S*)-10]

A solution of (*S*)-alpine borane (0.5 M in THF, 1.0 mL, 0.51 mmol) was introduced in a round-bottom flask and the solvent was removed under vacuum. A solution of **4** (75 mg, 0.24 mmol) in CH_2Cl_2 (0.4 mL) was then added dropwise at 0 °C, the solvent was removed under vacuum and the reaction mixture was stirred for 16 h at 20 °C. Et_2O (0.5 mL) and silica (100 mg) were added, the mixture was stirred for 1 h at room temperature and filtered. The solvent was removed under vacuum and the residue was purified by two successive flash chromatographies (cyclohexane/CH_2Cl_2/AcOEt: 75/20/5) then (cyclohexane/AcOEt: 95/5) to afford (*R*)-**10** as a white solid; yield: 53 mg (71%); mp 37 °C; $[\alpha]_D^{20}$: −42.6 (*c* 1.02, $CHCl_3$).

Compound (*S*)-10

Obtained from **4** (100 mg, 0.32 mmol) and (*R*)-alpine borane (1.36 mL, 0.68 mmol) following the procedure described for (*R*)-**10**. Purification of the residue by flash chromatography (cyclohexane/CH_2Cl_2/AcOEt: 75/20/5) then (cyclohexane/AcOEt: 95/5) afforded (*S*)-**10** as a white solid; yield: 77 mg (77%); $[\alpha]_D^{20}$: +40.5 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 4.84$ (dt, 1H, $J = 7.4$ and 2.2 Hz), 3.86 (s, 3H), 2.93 (d, 1H, $J = 7.4$ Hz), 2.21 (td, 2H, $J = 7.1$and 2.2 Hz), 1.56–1.44 (m, 2H), 1.25 (br s, 22H), 0.88 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 171.4$, 87.2, 75.4, 61.7, 53.5, 32.1, 29.8, 29.6, 29.5, 29.2, 29.0, 28.4, 27.0, 22.8, 18.8, 14.3; CSP-SFC (Chiralpak AD-H, 94:6 CO_2:methanol, 100 bar, 5.0 mL min^{-1}, $\lambda = 215$ nm): t_R 2.00 min, (*R*)-**10**; t_R 2.12 min, (*S*)-**10**.

(2*R*)-Ethyl 2-Hydroxyoctadec-3-ynoate [(*R*)-11] and (2*S*)-Ethyl 2-Hydroxyoctadec-3-ynoate [(*S*)-11]

A solution of (*S*)-alpine borane (0.5 M in THF, 6.51 mL, 3.25 mmol) was introduced in a round-bottom flask and the solvent was removed under vacuum. A solution of **5** (500 mg, 1.55 mmol) in CH_2Cl_2 (2 mL) was then added dropwise at 0 °C. The solvent was removed under vacuum and the reaction mixture was stirred for 16 h at 20 °C. Et_2O (3.5 mL) and silica (650 mg) were added, the mixture was stirred for 1 h at room temperature and filtered. The solvent was removed undervacuum and the residue was purified by two successive flash chromatographies (cyclohexane/CH_2Cl_2/AcOEt: 70/24/6) and (cyclohexane/AcOEt: 95/5) to afford (*R*)-**11** as a white solid; yield: 420 mg (83%); mp 40 °C; $[\alpha]_D^{20}$: −27.3 (*c* 0.74, $CHCl_3$).

Compound (*S*)-11

Obtained from **5** (500 mg, 1.55 mmol) and (*R*)-alpine borane (6.51 mL, 3.26 mmol) following the procedure described for (*R*)-**11**. Purification of the residue by flash chromatography (cyclohexane/CH_2Cl_2/AcOEt: 70/24/6) then (cyclohexane/AcOEt: 95/5) afforded (*S*)-**11** as a white solid; yield: 389 mg

(77%); $[\alpha]_D^{20}$: 26.1 (*c* 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.80 (dt, 1H, *J* = 7.3 and 2.1 Hz), 4.30 (q, 2H, *J* = 7.1 Hz), 3.00 (d, 1H, *J* = 7.3 Hz), 2.20 (td, 2H, *J* = 7.1 and 2.2 Hz), 1.56–1.43 (m, 2H), 1.33 (t, 3H, *J* = 7.1 Hz), 1.25 (br s, 22H), 0.87 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.0, 86.9, 75.7, 62.7, 61.7, 32.1, 29.8, 29.6, 29.5, 29.2, 28.9, 28.4, 22.8, 18.8, 14.3, 14.2; CSP-SFC (Chiralpak AD-H, 94:6 CO_2:methanol, 100 bar, 5.0 mL min^{-1}, λ = 215 nm): t_R 1.75 min, (*R*)-**11**; t_R 2.03 min, (*S*)-**11**; HR-MS (ESI): *m/z* = 347.2554, calcd. for $C_{20}H_{36}O_3Na$ $[M+Na]^+$: 347.2557.

(2*R*,3*Z*)-Ethyl 2-Hydroxyoctadec-3-enoate (12)

To a solution of **11** (409 mg, 1.26 mmol) in AcOEt (10 mL) were added Lindlar catalyst (134 mg, 0.063 mmol) and quinoline (48 μL, 0,40 mmol). The argon atmosphere was replaced with hydrogen and the reaction mixture was stirred at room temperature under hydrogen (balloon) for 2.5 h. The suspension was then filtered on a celite pad, the filtrate was concentrated under vacuum and the residue was purified by flash chromatography (cyclohexane/AcOEt: 9/1) to afford **12** as a white solid; yield: 355 mg (86%); mp 24 °C; $[\alpha]_D^{20}$: −140.0 (*c* 0.93, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.69 (dtd, 1H, *J* = 10.8, 7.5 and 1.2 Hz), 5.38–5.27 (m, 1H), 4.94–4.86 (m, 1H), 4.23 (dq, 2H, *J* = 7.1 and 1.2 Hz), 2.96 (d, 1H, *J* = 5.6 Hz), 2.24–2.12 (m, 2H), 1.47–1.34 (m, 2H), 1.28 (t, 3H, *J* = 7.1 Hz), 1.25 (br s, 22H), 0.87 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.3, 136.3, 126.2, 67.4, 62.1, 32.1, 29.8, 29.7, 29.5, 29.4, 28.1, 22.8, 14.3; HR-MS (ESI): *m/z* = 349.2711, calcd. for $C_{20}H_{38}O_3Na$ $[M+Na]^+$: 349.2713.

(2*R*,3*Z*)-2-Hydroxyoctadec-3-enoic Acid (13)

To a solution of **12** (308 mg, 0.94 mmol) in THF (8 mL) was added lithium hydroxide (434 mg, 10.3 mmol) in water/MeOH (5 mL/2.5 mL) at 0 °C. The mixture was stirred for 2 h at room temperature and aqueous HCl (1 M) was added at 0 °C. The aqueous layer was extracted with AcOEt and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum to afford **13** as a white solid; yield: 265 mg (94%); mp 60 °C; $[\alpha]_D^{20}$: −106.4 (*c* 1.08, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.77 (dt, 1H, *J* = 10.6 and 7.5 Hz), 5.44–5.32 (m, 1H), 5.02 (d, 1H, *J* = 8.7 Hz), 2.27–2.12 (m, 2H), 1.50–1.35 (m, 2H), 1.25 (br s, 22H), 0.88 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 178.7, 137.5, 125.1, 67.2, 32.1, 29.8, 29.7, 29.6, 29.5, 29.4, 28.2, 22.8, 14.3; HR-MS (ESI): *m/z* = 321.2401, calcd. for $C_{18}H_{34}O_3Na$ $[M+Na]^+$: 321.2400.

(2*R*,3*E*)-Octadec-3-ene-1,2-diol (14)

To a suspension of $LiAlH_4$ (328 mg, 8.64 mmol) in THF (27 mL) was added dropwise a solution of **11** (467 mg, 1.44 mmol) in THF (5 mL) at 0 °C. The mixture was stirred at room temperature for 1 h and then heated to reflux for 4 h. At 0 °C, a Rochelle salt solution and Et_2O were added, and the mixture was stirred for 1 h at room temperature. The aqueous layer was extracted with Et_2O and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum (heating bath temperature: 25 °C). Purification of the residue by flash chromatography (CH_2Cl_2/AcOEt: 8/2) afforded **14** as a white solid; yield: 245 mg (60%); $[\alpha]_D^{20}$: −11.0 (*c* 0.83, $CHCl_3$), lit.:[2b] $[\alpha]_D^{15}$: −8.97 (*c* 0.858, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.75 (dtd, 1H, *J* = 15.3, 6.7 and 1.0 Hz), 5.45 (ddt, 1H, *J* = 15.5, 6.6 and 1.4 Hz), 4.23–4.12 (m, 1H), 3.60 (dd, 1H, *J* = 11.2 and 2.9 Hz), 3.45 (dd, 1H, *J* = 11.2 and 7.8 Hz), 2.90 (br s, 2H), 2.02 (q *like*, 2H, *J* = 6.8 Hz), 1.40–1.28 (m, 2H), 1.24 (br s, 22H), 0.87 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 134.5, 128.3, 73.4, 66.8, 32.5, 32.1, 29.8, 29.6, 29.5, 29.4, 29.2, 22.8, 14.2.

(2*R*,3*E*)-1-*tert*-Butyldimethylsilyloxy-3-octadecen-2-ol (15)

To a solution of **14** (85 mg, 0.29 mmol) in CH_2Cl_2 (1 mL) were added *tert*-butyldimethylsilyl chloride (68 mg, 0.46 mmol), dimethylaminopyridine (3 mg, 0.029 mmol) and diisopropylethylamine (84 μL, 0.48 mmol). The mixture was stirred for 15 h at room temperature, then water was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, and concentrated under vacuum. Purification of the residue by flash chromatography (cyclohexane/diisopropyl ether: 93/7) afforded **15** as a colorless oil; yield: 100 mg (89%); $[\alpha]_D^{20}$: −13.6 (*c* 0.98, $CHCl_3$), lit.:[3] $[\alpha]_D^{23}$: −11.4 (*c* 1.33, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 5.75 (dtd, 1H, *J* = 15.5, 6.8 and 0.9 Hz), 5.38 (ddt, 1H, *J* = 15.4, 6.7 and 1.4 Hz), 4.16–4.05 (m, 1H), 3.61 (dd, 1H, *J* = 10.0 and 3.6 Hz), 3.41 (dd, 1H, *J* = 9.9 and 8.1 Hz), 2.56 (d, 1H, *J* = 6.9 Hz), 2.02 (q *like*, 2H, *J* = 6.9 Hz), 1.40–1.28 (m, 2H), 1.25 (br s, 22H), 0.90 (s, 9H), 0.87 (t, 3H, *J* = 6.7 Hz), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 134.2, 128.1, 73.0, 67.5, 32.5, 32.1, 29.8, 29.6, 29.5, 29.3, 29.2, 27.1, 26.0, 22.8, 18.4, 14.2, −5.2.

(2*R*,3*E*)-1-*tert*-Butyldimethylsilyloxy-2-*tert*-butyldiphenylsilyloxy-3-octadecene (16)

To a solution of **15** (430 mg, 1.08 mmol) in DMF (4.5 mL) were added imidazole (360 mg, 5.28 mmol) and *tert*-butyldiphenylsilyl chloride (813 μL, 3.13 mmol). The mixture was stirred at room temperature for 3 h. Brine was added, the aqueous layer was extracted with AcOEt, the combined organic layers were dried over $MgSO_4$, concentrated under vacuum and the residue was purified by flash chromatography (cyclohexane/diisopropyl ether: 99/1) to afford **16** as a colorless oil; yield: 621 mg (90%); $[\alpha]_D^{20}$: −14.1 (*c* 0.96, $CHCl_3$), lit.:[3] $[\alpha]_D^{23}$: −13.3 (*c* 1.66, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.69 (tt, 4H, *J* = 7.9 and 1.9 Hz), 7.46–7.30 (m, 6H), 5.45–5.30 (m, 2H), 4.13 (q *like*, 1H, *J* = 5.7 Hz), 3.57 (dd, 1H, *J* = 9.9 and 5.8 Hz), 3.43 (dd, 1H, *J* = 9.9 and 6.5, Hz), 1.98–1.81 (m, 2H), 1.27 (br s, 24H), 1.07 (s, 9H), 0.89 (t, 3H, *J* = 6.6 Hz), 0.84 (s, 9H), −0.04 (s, 3H), −0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.2, 136.1, 134.6, 134.5, 132.8, 130.4, 129.6, 129.5, 127.5, 127.4, 75.2, 67.9, 32.4, 32.1, 29.9, 29.8, 29.7, 29.5, 29.3, 29.2, 27.2, 26.1, 22.9, 19.5, 18.5, 14.3, −5.2.

(2*R*,3*E*)-2-*tert*-Butyldiphenylsilyloxy-3-octadecen-1-ol (17)

A solution of **16** (615 mg, 0.97 mmol) in AcOH/THF/H_2O:3/1/1 (15 mL) was stirred at 70 °C for 24 h. AcOEt and saturated $NaHCO_3$ were then added. The aqueous layer was ex-

tracted with AcOEt and the combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under vacuum. Purification of the residue was purified by flash chromatography (cyclohexane/diisopropyl ether: 95/5) afforded **17** as a colorless oil; yield: 306 mg (61%); $[\alpha]_D^{20}$: −40.0 (*c* 0.98, $CHCl_3$), lit.:[3] $[\alpha]_D^{23}$: −38.1 (*c* 1.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.68 (ddd, 4H, *J* = 7.9, 3.0 and 1.6 Hz), 7.47–7.32 (m, 6H), 5.38 (dd *like*, 2H, *J* = 5.4 and 2.4 Hz), 4.26–4.16 (m, 1H), 3.57–3.39 (m, 2H), 1.96–1.78 (m, 3H), 1.27 (br s, 24H), 1.08 (s, 9H), 0.89 (t, 3H, *J* = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 136.1, 135.9, 134.4, 134.1, 133.9, 129.9, 129.8, 129.0, 127.8, 127.6, 75.4, 67.2, 32.3, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 29.0, 27.2, 27.1, 22.8, 19.5, 14.3.

(2*R*,3*E*)-2-*tert*-Butyldiphenylsilyloxy-3-octadecenoic Acid (18)

Jones's reagent (8N, 614 μL) was added slowly to a stirred solution of **17** (306 mg, 0.59 mmol) in acetone (3.4 mL) at 0 °C. The mixture was stirred at 0 °C for 4 h and poured onto ice/water. The aqueous layer was extracted with AcOEt and the combined organic layers were washed with brine, dried over $MgSO_4$, concentrated under vacuum. Purification of the residue by flash chromatography (cyclohexane/diisopropyl ether: 8/2) afforded **18** as a colorless oil; yield: 255 mg (81%); $[\alpha]_D^{20}$: −33.0 (*c* 1.03, $CHCl_3$), lit.:[3] $[\alpha]_D^{23}$: −34.1 (*c* 1.16, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.60–7.51 (m, 4H), 7.41–7.25 (m, 6H), 5.53 (dt, 1H, *J* = 15.4 and 6.7 Hz), 5.35 (dd, 1H, *J* = 15.4 and 6.6 Hz), 4.55 (d, 1H, *J* = 6.4 Hz), 1.91 (q *like*, 2H, *J* = 6.4 Hz), 1.26 (br s, 24H), 1.12 (s, 9H), 0.88 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 175.1, 135.9, 134.9, 132.7, 132.4, 130.3, 130.2, 128.0, 127.9, 127.8, 74.1, 32.2, 32.1, 29.8, 29.7, 29.6, 29.5, 29.3, 28.8, 27.0, 26.7, 22.8, 19.4, 14.3.

(2*R*,3*R*)-Methyl 2-Amino-3-hydroxyoctadecanoate (19) and (2*S*,3*S*)-Methyl 2-Amino-3-hydroxyoctadecanoate [(*ent*)-19]

To the complex [Ru((*R*)-SYNPHOS)Br_2] (0.14 mmol, 0.02 equiv., prepared according to the general procedure) was added **5** (2.5 g, 6.87 mmol) followed by degassed anhydrous CH_2Cl_2 (18 mL) and MeOH (2 mL). The round-bottom flask was degassed by three vacuum-argon cycles and then placed under argon in a stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 12 bar. The autoclave was heated at 50 °C and stirring was maintained for 24 h. After cooling, the reaction mixture was concentrated under reduced pressure to afford the crude α-amino-β-hydroxy ester hydrochloride.

To a solution of the above crude product in Et_2O/MeOH (80 mL/8 mL) was added triethylamine (6.76 mL, 48.1 mmol). The mixture was stirred at room temperature for 2 h, filtered and the filtrate was concentrated under vacuum. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH: 95/5) afforded **19** as a pale pink solid; yield: 1.50 g (66%); mp 56 °C; $[\alpha]_D^{20}$: −31.3 (*c* 0.46, $CHCl_3$).

Compound (*ent*)-19

Obtained from **5** (1.0 g, 2.75 mmol) according to the general procedure with [Ru((*S*)-SYNPHOS)Br_2]. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH: 95/5) afforded (*ent*)-**19** as a pale pink solid; yield: 535 mg (59%); $[\alpha]_D^{20}$: +30.5 (*c* 0.85, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.81–3.74 (m, 1H), 3.73 (s, 3H), 3.56 (d, 1H, *J* = 4.5 Hz), 2.52 (br s, 3H), 1.55–1.36 (m, 2H), 1.24 (br s, 26H), 0.86 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 174.5, 72.5, 58.7, 52.2, 32.5, 32.0, 29.8, 29.7, 29.5, 25.9, 22.8, 14.2.

The diastereo- and enantiomeric excesses were determined by HPLC after conversion of the crude hydrogenated products into the corresponding methyl (2*R*,3*R*)-2-benzoylamino-3-hydroxyoctadecanoate **19′** and methyl (2*S*,3*S*)-2-benzoylamino-3-hydroxyoctadecanoate (*ent*)-**19′**, respectively. HPLC (Chiralpak AS-H, 98:2 hexane:2-propanol, 1.0 mL min^{-1}, λ = 254 nm): t_R 26.37 min, **19′**, t_R 32.31 min, (*ent*)-**19′**.

(2*S*,3*R*)-1,3-*O*-Isopropylidene-[2-amino-1,3-dihydroxyoctadecane] (20) and (2*R*,3*S*)-1,3-*O*-Isopropylidene-[2-amino-1,3-dihydroxyoctadecane] [(*ent*)-20]

To a suspension of $LiAlH_4$ (87 mg, 2.30 mmol) in THF (4 mL) was added dropwise a solution of **19** (505 mg, 1.53 mmol) in THF (4 mL) at 0 °C. The mixture was stirred for 2 h at room temperature, then cooled to 0 °C, and silica (90 mg), water (90 μL), a 10% aqueous solution of sodium hydroxide (90 μL) and again water (270 μL) were added. The resulting mixture was stirred at 0 °C for 30 min and filtered. The filtrate was concentrated under vacuum and the crude amino-diol was dissolved in $CHCl_3$ (14 mL). Dimethoxypropane (2.8 mL, 22.3 mmol) and PPTS (384 mg, 1.53 mmol) were added and the reaction mixture was stirred for 2 h under reflux. $CHCl_3$ and saturated $NaHCO_3$ were added. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH: 96/4) afforded **20** as a white solid; yield: 325 mg (62%); mp 32 °C, lit.:[4] mp 36–37 °C, lit.:[3] mp 61–62 °C; $[\alpha]_D^{20}$: +29.2 (*c* 1.3, $CHCl_3$), lit.:[2b] $[\alpha]_D^{22}$: +29.5 (*c* 1.178, $CHCl_3$), lit.:[4] $[\alpha]_D^{25}$: +31.7 (*c* 1.03, $CHCl_3$), lit.:[3] $[\alpha]_D^{21}$: +32.4 (*c* 1.08, $CHCl_3$).

Compound (*ent*)-20

Obtained from (*ent*)-**19** (300 mg, 0.91 mmol). Purification of the residue by flash chromatography (CH_2Cl_2/MeOH: 96/4) afforded (*ent*)-**20** as a white solid; yield: 159 mg (51%); $[\alpha]_D^{20}$: −32.0 (*c* 0.84, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.80 (dd, 1H, *J* = 11.3 and 5.3 Hz), 3.44 (dd, 1H, *J* = 11.3 and 9.9 Hz), 3.43–3.33 (m, 1H), 2.62 (td, 1H, *J* = 9.7 and 5.3 Hz), 1.78–1.64 (m, 2H), 1.42 (s, 3H), 1.37 (s, 3H), 1.24 (br s, 26H), 1.06 (br s, 2H), 0.86 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 98.5, 75.8, 66.4, 49.9, 32.4, 32.1, 29.8, 29.5, 29.2, 25.2, 22.8, 19.4, 14.3.

(2*S*,3*R*,2′*R*,3′*E*)-2-*N*-(2′-*tert*-Butyldiphenylsilyloxy-3′-octadecenoyl)-1,3-*O*-isopropylidene-[2-aminooctadecane-1,3-diol] (21)

To a solution of **20** (31 mg, 0.09 mmol) and **18** (59 mg, 0.11 mmol) in CH_2Cl_2 (1.5 mL) were added HATU (41 mg, 0.11 mmol) and diisopropylamine (47 μL, 0.27 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C and filtered on a silica pad. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography (cyclohexane/diisopropyl ether: 8/2) to afford **21** as a colorless oil; yield: 50 mg (64%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.65–7.57 (m, 4H), 7.49–7.32 (m, 6H), 6.54 (d, 1H, J = 9.0 Hz), 5.66 (dtd, 1H, J = 15.3, 6.7 and 1.1 Hz), 5.45 (dd, 1H, J = 15.4 and 6.0 Hz), 4.58 (dd, 1H, J = 6.0 and 0.9 Hz), 3.82–3.67 (m, 2H), 3.55–3.42 (m, 1H), 3.26 (dd, 1H, J = 13.0 and 9.9 Hz), 1.95 (q *like*, 2H, J = 6.2 Hz), 1.58–1.40 (m, 2H), 1.39 (s, 3H), 1.38 (s, 3H), 1.26 (br s, 50H), 1.14 (s, 9H), 0.88 (t, 6H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.9, 135.9, 135.7, 134.5, 132.8, 132.5, 130.4, 130.3, 128.1, 127.9, 127.2, 98.9, 75.5, 72.7, 62.9, 47.9, 32.9, 32.2, 29.9, 29.7, 29.5, 29.3, 29.1, 28.2, 27.1, 25.3, 22.8, 20.1, 19.4, 14.3.

(2*R*,3*S*,2′*R*,3′*E*)-2-*N*-(2′-*tert*-Butyldiphenylsilyloxy-3′-octadecenoyl)-1,3-*O*-isopropylidene-[2-aminooctadecane-1,3-diol] (22)

Obtained from (*ent*)-**20** (32 mg, 0.09 mmol) and **18** (60 mg, 0.11 mmol) following the procedure described for compound **21**. Purification of the residue by flash chromatography (cyclohexane/diisopropyl ether: 88/12) afforded **22** as a colorless oil; yield: 60 mg (74%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.61 (ddd, 4H, J = 7.9, 5.3 and 1.5 Hz), 7.47–7.32 (m, 6H), 6.71 (d, 1H, J = 9.0 Hz), 5.54 (dt, 1H, J = 15.4 and 6.7 Hz), 5.40 (dd, 1H, J = 15.4 and 6.4 Hz), 4.56 (d, 1H, J = 6.3 Hz), 3.91 (dd, 1H, J = 11.3 and 5.2 Hz), 3.85–3.73 (m, 1H), 3.52 (dd, 1H, J = 11.3 and 7.3 Hz), 3.50–3.40 (m, 1H), 1.90 (q *like*, 2H, J = 6.3 Hz), 1.49–1.29 (m, 2H), 1.43 (s, 3H), 1.42 (s, 3H), 1.27 (br s, 50H), 1.13 (s, 9H), 0.89 (t, 6H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.1, 135.9, 135.7, 134.9, 132.8, 132.6, 130.3, 130.2, 128.1, 127.8, 127.1, 99.2, 75.8, 72.5, 63.2, 48.6, 33.1, 32.2, 32.1, 29.8, 29.6, 29.5, 29.3, 28.9, 27.7, 27.1, 26.7, 25.4, 22.8, 20.6, 19.5, 14.3.

(2*S*,3*R*,2′*R*,3′*E*)-2-*N*-(2′-*tert*-Butyldiphenylsilyloxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (23)

To a solution of **21** (48 mg, 0.056 mmol) in CH_2Cl_2/MeOH (0.5 mL/0.5 mL) was added PTSA (1.7 mg, 0.008 mmol). The mixture was stirred for 2.5 h at room temperature and saturated $NaHCO_3$ was added. The aqueous layer was extracted with AcOEt. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 8/2) afforded **23** as a white solid; yield: 30 mg (66%); $[\alpha]_D^{20}$: +0.8 (*c* 1.00, $CHCl_3$), lit.:[4] $[\alpha]_D^{20}$: +2.02 (*c* 0.945, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.63 (ddd, 4H, J = 14.8, 7.9 and 1.4 Hz), 7.55 (d, 1H, J = 7.6 Hz), 7.48–7.30 (m, 6H), 5.64 (dtd, 1H, J = 15.3, 6.7 and 0.8 Hz), 5.47 (dd, 1H, J = 15.4 and 6.1 Hz), 4.62 (d, 1H, J = 5.8 Hz), 3.89 (dd, 1H, J = 11.2 and 2.1 Hz), 3.77–3.65 (m, 2H), 3.57 (d *like*, 1H, J = 11.0 Hz), 2.56 (br s, 1H), 2.28 (br s, 1H), 2.01–1.87 (m, 2H), 1.79–1.58 (m, 2H), 1.25 (br s, 50H), 1.14 (s, 9H), 0.88 (t, 6H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.6, 136.0, 135.8, 134.7, 133.1, 132.8, 130.3, 130.2, 128.0, 127.8, 127.3, 75.6, 73.9, 62.7, 53.7, 34.6, 32.2, 32.1, 30.3, 29.8, 29.5, 29.3, 29.0, 27.1, 26.1, 22.8, 19.3, 14.3.

(2*R*,3*S*,2′*R*,3′*E*)-2-*N*-(2′-*tert*-Butyldiphenylsilyloxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (24)

Obtained from **22** (58 mg, 0.067 mmol) following the procedure described for compound **23**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 9/1 to 8/2) afforded **24** as a white solid; yield: 36 mg (65%). $[\alpha]_D^{20}$: −8.7 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.63 (ddd, 4H, J = 16.1, 7.9 and 1.4 Hz), 7.56 (d, 1H, J = 7.7 Hz), 7.48–7.31 (m, 6H), 5.63 (dtd, 1H, J = 15.3, 6.8 and 0.8 Hz), 5.47 (dd, 1H, J = 15.4 and 6.2 Hz), 4.63 (d, 1H, J = 5.8 Hz), 4.04–3.91 (m, 1H), 3.74–3.62 (m, 2H), 3.62–3.51 (m, 1H), 2.78 (br s, 1H), 2.25 (br s, 1H), 2.00–1.87 (m, 2H), 1.54–1.40 (m, 2H), 1.26 (br s, 50H), 1.14 (s, 9H), 0.88 (t, 6H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.6, 136.0, 135.8, 134.8, 133.1, 132.8, 130.3, 130.2, 128.0, 127.7, 127.3, 75.7, 74.1, 62.4, 53.9, 34.5, 32.2, 32.1, 29.9, 29.5, 29.3, 29.0, 27.1, 26.1, 22.8, 19.3, 14.3.

(2*S*,3*R*,2′*R*,3′*E*)-2-*N*-(2′-hydroxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol]: Symbioramide (1)

To a solution of **23** (29 mg, 0.035 mmol) in THF (2.2 mL) was added tetrabutylamonium fluoride (1 M in THF, 51 μL, 0.051 mmol). The mixture was stirred for 1 h at room temperature, then poured onto water. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography ($CHCl_3$/MeOH: 96/4) afforded **1** as a white solid; yield: 17 mg (83%); mp 104 °C; $[\alpha]_D^{20}$: +4.7 (*c* 0.29, $CHCl_3$), lit.:[1] $[\alpha]_D^{20}$: +5.8 (*c* 1, $CHCl_3$), lit.:[2b] $[\alpha]_D^{20}$: +2.65 (*c* 0.378, $CHCl_3$), lit.:[3] $[\alpha]_D^{20}$: +1.19 (*c* 0.5, $CHCl_3$), lit.:[4] $[\alpha]_D^{20}$: +3.6 (*c* 0.31, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C): δ = 6.92 (d, 1H, J = 7.2 Hz), 5.90 (dtd, 1H, J = 15.3, 7.2 and 0.6 Hz), 5.59 (ddt, 1H, J = 15.4, 6.9 and 1.3 Hz), 4.53 (d, 1H, J = 6.9 Hz), 4.00 (dd, 1H, J = 11.2 and 3.4 Hz), 3.87–3.74 (m, 3H), 3.02 (br s, 1H), 2.51 (br s, 1H), 2.41 (br s, 1H), 2.10 (q *like*, 2H, J = 6.9 Hz), 1.59–1.48 (m, 2H), 1.47–1.37 (m, 2H), 1.29 (br s, 48H), 0.90 (t, 6H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C): δ = 173.0, 136.3, 128.0, 74.1, 73.4, 62.5, 54.8, 34.8, 32.4, 32.1, 29.9, 29.8, 29.5, 29.4, 26.1, 22.8, 14.1.

(2*R*,3*S*,2′*R*,3′*E*)-2-*N*-(2′-Hydroxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (25)

Obtained from **24** (34 mg, 0.041 mmol) following the procedure described for compound **1**. Purification of the residue by flash chromatography ($CHCl_3$/MeOH: 95/5) afforded **25** as a white solid; yield: 18 mg (75%); $[\alpha]_D^{20}$: +76.1 (*c* 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C): δ = 6.87 (d, 1H, J = 7.0 Hz), 5.90 (dtd, 1H, J = 15.4, 6.9 and 1.0 Hz), 5.58 (ddt, 1H, J = 15.3, 7.0 and 1.4 Hz), 4.52 (d, 1H, J = 7.0 Hz), 4.00 (dd, 1H, J = 11.3 and 3.4 Hz), 3.87–3.71 (m, 3H), 2.96 (br s, 1H), 2.44 (br s, 1H), 2.38 (br s, 1H), 2.10 (q *like*, 2H, J = 6.9 Hz), 1.61–1.48 (m, 2H), 1.48–1.34 (m, 2H), 1.29 (br s, 48H), 0.90 (t, 6H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz,

50 °C): δ = 173.0, 136.4, 128.1, 74.1, 73.4, 62.5, 54.8, 34.7, 32.4, 32.1, 29.9, 29.8, 29.5, 29.4, 29.2, 26.1, 22.8, 14.1.

(2*S*,3*R*,2′*R*,3′*Z*)-2-*N*-(2′-Hydroxy-3′-octadecenoyl)-1,3-*O*-isopropylidene-[2-amino-octadecane-1,3-diol] (26)

To a solution of **20** (50 mg, 0.15 mmol) and **13** (52 mg, 0.18 mmol) in CH_2Cl_2 (2.5 mL) were added HATU (67 mg, 0.18 mmol) and diisopropylamine (76 μL, 0.44 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C and filtered on a silica pad. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography (cyclohexane/AcOEt: 83/17) to afford **26** as a white solid; yield: 55 mg (60%); mp 60 °C; $[\alpha]_D^{20}$: −53.9 (*c* 0.78, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.19 (d, 1H, *J* = 9.0 Hz), 5.78 (dt, 1H, *J* = 10.2 and 7.9 Hz), 5.39 (dd, 1H, *J* = 10.7 and 9.1 Hz), 4.83 (d, 1H, *J* = 8.9 Hz), 3.97–3.76 (m, 2H), 3.63–3.48 (m, 2H), 2.98 (br s, 1H), 2.27–2.12 (m, 2H), 1.58–1.36 (m, 4H), 1.42 (s, 3H), 1.38 (s, 3H), 1.25 (br s, 48H), 0.87 (t, 6H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.4, 137.4, 126.9, 99.2, 72.4, 68.3, 63.1, 48.9, 32.9, 32.1, 29.8, 29.7, 29.5, 28.1, 28.0, 25.3, 22.8, 20.4, 14.3; HR-MS (ESI): *m/z* = 644.5589, calcd. for $C_{39}H_{75}ONNa$ $[M+Na]^+$: 644.5588.

(2*R*,3*S*,2′*R*,3′*Z*)-2-*N*-(2′-Hydroxy-3′-octadecenoyl)-1,3-*O*-isopropylidene-[2-aminooctadecane-1,3-diol] (27)

Obtained from (*ent*)-**20** (50 mg, 0.15 mmol) and **13** (52 mg, 0.18 mmol) following the procedure described for compound **26**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 8/2) afforded **27** as a white solid; yield: 59 mg (65%); $[\alpha]_D^{20}$: −68.5 (*c* 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 6.17 (d, 1H, *J* = 8.9 Hz), 5.77 (dtd, 1H, *J* = 10.7, 7.5 and 0.8 Hz), 5.45–5.33 (m, 1H), 4.82 (dd, 1H, *J* = 9.0 and 2.3 Hz), 3.95–3.77 (m, 2H), 3.62–3.46 (m, 2H), 3.01 (d, 1H, *J* = 3.3 Hz), 2.28–2.12 (m, 2H), 1.57–1.35 (m, 4H), 1.42 (s, 3H), 1.38 (s, 3H), 1.25 (br s, 50H), 0.87 (t, 6H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.4, 137.3, 127.0, 99.2, 72.2, 68.2, 63.1, 48.9, 32.9, 32.1, 29.8, 29.7, 29.5, 28.1, 27.9, 25.2, 22.8, 20.4, 14.3.

(2*S*,3*R*,2′*R*,3′*Z*)-2-*N*-(2′-hydroxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (28)

To a solution of **26** (48 mg, 0.077 mmol) in CH_2Cl_2/MeOH (0.5 mL/0.5 mL) was added PTSA (2.0 mg, 0.011 mmol). The mixture was stirred for 1.5 h at room temperature and saturated $NaHCO_3$ was added. The aqueous layer was extracted with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography ($CHCl_3$/MeOH: 95/5) afforded **28** as a white solid; yield: 29 mg (64%); $[\alpha]_D^{20}$: −48.7 (*c* 0.34, $CHCl_3$), lit.:[3] $[\alpha]_D^{20}$: −49.9 (*c* 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C): δ = 6.92 (d, 1H, *J* = 7.1 Hz), 5.78 (dt, 1H, *J* = 11.4 and 7.5 Hz), 5.46 (dd, 1H, *J* = 10.6 and 8.9 Hz), 4.88 (d, 1H, *J* = 8.8 Hz), 3.99 (dd, 1H, *J* = 11.2 and 3.5 Hz), 3.87–3.72 (m, 3H), 3.01 (br s, 1H), 2.52 (br s, 1H), 2.42 (br s, 1H), 2.28–2.18 (m, 2H), 1.60–1.49 (m, 2H), 1.49–1.40 (m, 2H), 1.29 (s, 48H), 0.90 (t, 6H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C): δ = 173.1, 137.1, 127.4, 74.1, 68.7, 62.4, 54.8, 34.8, 32.1, 29.9, 29.8, 29.5, 28.2, 26.1, 22.8, 14.3.

(2*R*,3*S*,2′*R*,3′*Z*)-2-*N*-(2′-Hydroxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (29):

Obtained from **27** (55 mg, 0.088 mmol) following the procedure described for compound **28**. Purification of the residue by flash chromatography ($CHCl_3$/MeOH: 95/5) afforded **29** as a white solid; yield: 43 mg (83%); $[\alpha]_D^{20}$: −73.4 (*c* 0.32, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C): δ = 6.91 (d, 1H, *J* = 7.2 Hz), 5.77 (dt, 1H, *J* = 10.6 and 7.4 Hz), 5.46 (dd, 1H, *J* = 10.6 and 9.0 Hz), 4.87 (d, 1H, *J* = 8.7 Hz), 3.99 (dd, 1H, *J* = 11.7 and 3.5 Hz), 3.87–3.70 (m, 3H), 3.06 (br s, 1H), 2.58 (br s, 1H), 2.52 (br s, 1H), 2.30–2.16 (m, 2H), 1.61–1.50 (m, 2H), 1.50–1.40 (m, 2H), 1.29 (br s, 48H), 0.90 (t, 6H, *J* = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C): δ = 173.2, 137.0, 127.5, 74.0, 68.7, 62.4, 54.9, 34.7, 32.1, 29.8, 29.5, 28.2, 26.1, 22.8, 14.3; HR-MS (ESI): *m/z* = 604.5270, calcd. for $C_{36}H_{71}NO_4Na$ $[M+Na]^+$: 604.5275.

(2*S*,3*R*)-Methyl 2-Benzoylamino-3-hydroxyoctadecanoate (31) and (2*R*,3*S*) Methyl 2-Benzoylamino-3-hydroxyoctadecanoate [(*ent*)-31]

To the complex [Ru((*R*)-SYNPHOS)Br_2] (0.009 mmol, 0.02 equiv., prepared according to the general procedure) was added **30** (200 mg, 0.46 mmol) followed by degassed anhydrous CH_2Cl_2 (3 mL). The round-bottom flask was degassed by three vacuum-argon cycles and then placed under argon in a stainless steel autoclave. The argon atmosphere was replaced with hydrogen by three cycles of pressurizing and the pressure adjusted to 60 bar. The autoclave was heated at 80 °C and stirring was maintained for 4 days. After cooling, the reaction mixture was concentrated under reduced pressure and the residue was purified by flash chromatography (cyclohexane/AcOEt: 8/2) afforded **31** as a white solid; yield: 176 mg (88%); mp 72 °C, lit.:[7b] mp 72 °C; $[\alpha]_D^{20}$: +6.0 (*c* 1.0, $CHCl_3$), lit.:[7b] $[\alpha]_D^{21}$: +6.0 (*c* 1.0, $CHCl_3$).

Compound (*ent*)-31

Obtained from **30** (400 mg, 0.93 mmol) with [Ru((*S*)-SYNPHOS)Br_2] following the procedure described for compound **31**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 8/2) afforded (*ent*)-**31** as a white solid; yield: 331 mg, (82%); $[\alpha]_D^{20}$: −7.0 (*c* 1.0, $CHCl_3$), lit.:[7b] $[\alpha]_D^{21}$: −7.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.89–7.80 (m, 2H), 7.56–7.39 (m, 3H), 6.94 (br d, *J* = 8.8 Hz), 4.88 (dd, 1H, *J* = 8.9 and 1.8 Hz), 4.29–4.18 (m, 1H), 3.79 (s, 3H), 1.60–1.42 (m, 2H), 1.25 (br s, 26H), 0.87 (t, 3H, *J* = 6.6 Hz).^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.1, 167.9, 133.9, 132.0, 128.8, 128.4, 72.3, 56.5, 52.8, 34.0, 32.1, 29.8, 29.7, 29.5, 25.8, 22.8, 14.3; HPLC (Chiralpak AS-H, 98:2 hexane:2–propanol, 1.0 mL min^{-1}, λ = 254 nm): t_R 24.13 min, (*ent*)-**31**, t_R 29.59 min, **31**.

(2*S*,3*R*)-2-Benzoylamino-3-hydroxyoctadecan-1-ol (32) and (2*R*,3*S*)-2-Benzoylamino-3-hydroxyoctadecan-1-ol [(*ent*)-32]

To suspension of $LiAlH_4$ (136 mg, 3.58 mmol) in THF (2.5 mL) was added dropwise a solution of **31** (485 mg, 1.12 mmol) in THF (5 mL) at 0 °C. The mixture was stirred for 4 h under reflux, then EtOAc (5 mL) and water (5 mL) were added at room temperature. The mixture was filtered on a celite pad and the aqueous layer was extracted with

CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH: 95/5) afforded **32** as a white solid; yield: 344 mg (79%); mp 46 °C; $[\alpha]_D^{20}$: −5.6 (*c* 0.96, $CHCl_3$).

Compound (*ent*)-32

Obtained from (*ent*)-**31** (570 mg, 1.31 mmol) following the procedure described for compound **32**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 8/2) afforded (*ent*)-**32** as a white solid; yield: 349 mg (68%); $[\alpha]_D^{20}$: +6.4 (*c* 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.38–7.22 (m, 5H), 3.92 (d, 1H, *J* = 13.0 Hz), 3.79 (d, 1H, *J* = 13.0 Hz), 3.77 (dd, 1H, *J* = 11.2 and 3.9 Hz), 3.59 (dd, 1H, *J* = 11.3 and 3.8 Hz), 3.66–3.56 (m, 1H), 2.90 (br s, 3H), 2.54 (dd, 1H, *J* = 9.2 and 3.8 Hz), 1.58–1.36 (m, 2H), 1.26 (br s, 24H), 0.87 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 139.7, 128.7, 128.4, 127.5, 72.0, 61.8, 61.4, 52.1, 34.6, 32.1, 29.8, 29.5, 25.9, 22.8, 14.3.

(2*R*,3*R*)-1,3-*O*-Isopropylidene-[2-amino-1,3-dihydroxyoctadecane] (33) and (2*S*,3*S*)-1,3-*O*-Isopropylidene-[2-amino-1,3-dihydroxyoctadecane] [(*ent*)-33]

To a solution of **32** (200 mg, 0.51 mmol) in EtOH (5 mL) was added Pd/C (10%, 54 mg, 0.051 mmol). The argon atmosphere was replaced with hydrogen and the reaction mixture was stirred at room temperature under hydrogen (balloon) for 20 h. The suspension was then filtered on a celite pad and washed with CH_2Cl_2. The filtrate was concentrated under vacuum and the residue was dissolved in $CHCl_3$ (4 mL). Dimethoxypropane (0.94 mL, 7.65 mmol) and PPTS (128 mg, 0.51 mmol) were added and the reaction mixture was stirred for 2 h under reflux. $CHCl_3$ and saturated $NaHCO_3$ were added. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH: 96/4) afforded **33** as a white solid; yield: 100 mg (57%); mp 33 °C. $[\alpha]_D^{20}$: +6.9 (*c* 0.71, $CHCl_3$).

Compound (*ent*)-33

Obtained from (*ent*)-**32** (170 mg, 0.43 mmol) following the procedure described for compound **33**. Purification of the residue by flash chromatography (CH_2Cl_2/MeOH: 96/4) afforded (*ent*)-**33** as a white solid; yield: 99 mg (67%); $[\alpha]_D^{20}$: −9.7 (*c* 0.67, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 4.08 (dd, 1H, *J* = 11.7 and 2.1 Hz), 3.86–3.79 (m, 1H), 3.71 (dd, 1H, *J* = 11.7 and 1.8 Hz), 2.47 (q, 1H, *J* = 1.8 Hz), 1.69 (br s, 2H), 1.55–1.44 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 1.24 (br s, 26H), 0.86 (t, 3H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 98.8, 72.1, 67.5, 47.8, 32.0, 29.9, 29.8, 29.7, 29.5, 25.2, 22.8, 18.8, 14.3.

(2*R*,3*R*,2′*R*,3′*E*)-2-*N*-(2′-*tert*-Butyldiphenylsilyloxy-3′-octadecenoyl)-1,3-*O*-isopropylidene-[2-aminooctadecane-1,3-diol] (34)

Obtained from **33** (37 mg, 0.11 mmol) and **18** (70 mg, 0.13 mmol) following the procedure described for compound **21**. Purification of the residue by flash chromatography (cyclohexane/diisopropyl ether: 8/2) afforded **34** as a colorless oil; yield: 70 mg (75%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.69 (d, 1H, *J* = 12.9 Hz), 7.66 (ddd, 4H, *J* = 8.0, 4.9 and 1.5 Hz), 7.46–7.31 (m, 6H), 5.47–5.31 (m, 2H), 4.60 (d, 1H, *J* = 5.6 Hz), 4.10 (dd, 1H, *J* = 11.9 and 1.6 Hz), 4.00–3.91 (m, 1H), 3.85 (dd, 1H, *J* = 9.8 and 1.5 Hz), 3.72 (dd, 1H, *J* = 11.9 and 1.6 Hz), 1.91–1.76 (m, 2H), 1.48 (s, 3H), 1.40 (s, 3H), 1.26 (br s, 52H), 1.14 (s, 9H), 0.88 (t, 6H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 172.1, 136.1, 135.9, 135.5, 133.1, 132.8, 130.1, 130.0, 127.9, 127.7, 127.3, 99.2, 75.9, 71.5, 65.7, 45.4, 32.2, 32.1, 30.3, 29.8, 29.7, 29.5, 29.3, 28.7, 27.2, 27.0, 25.0, 22.8, 19.4, 18.7, 14.3.

(2*S*,3*S*,2′*R*,3′*E*)-2-*N*-(2′-*tert*-Butyldiphenylsilyloxy-3′-octadecenoyl)-1,3-*O*-isopropylidene-[2-aminooctadecan-1,3-diol] (35)

Obtained from (*ent*)-**33** (26 mg, 0.08 mmol) and **18** (50 mg, 0.09 mmol) following the procedure described for compound **21**. Purification of the residue by flash chromatography (cyclohexane/diisopropyl ether: 8/2 to 7/3) afforded **35** as a colorless oil; yield: 44 mg (68%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.66 (ddd, 4H, *J* = 7.9, 2.9 and 1.5 Hz), 7.58 (d, 1H, *J* = 9.9 Hz), 7.46–7.31 (m, 6H), 5.60 (dtd, 1H, *J* = 15.4, 6.6 and 0.8 Hz), 5.44 (dd, 1H, *J* = 15.4 and 6.1 Hz), 4.58 (d, 1H, *J* = 5.7 Hz), 4.06 (dd, 1H, *J* = 11.9 and 1.7 Hz), 3.99–3.91 (m, 1H), 3.79 (dd, 1H, *J* = 9.9 and 1.5 Hz), 3.60 (dd, 1H, *J* = 12.0 and 1.5 Hz), 1.96–1.80 (m, 2H), 1.78–1.56 (m, 2H), 1.47 (s, 3H), 1.35 (s, 3H), 1.26 (br s, 50H), 1.15 (s, 9H), 0.88 (t, 6H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 171.9, 136.0, 135.9, 134.3, 133.0, 132.7, 130.2, 130.0, 127.9, 127.7, 127.7, 99.1, 75.5, 71.3, 65.0, 44.9, 32.2, 32.1, 32.0, 30.3, 30.0, 29.6, 29.5, 29.4, 29.0, 27.2, 27.0, 24.8, 22.8, 19.4, 18.8, 14.3.

(2*R*,3*R*,2′*R*,3′*E*)-2-*N*-(2′-*tert*-Butyldiphenylsilyloxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (36)

Obtained from **34** (67 mg, 0.078 mmol) following the procedure described for compound **23**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 8/2) afforded **36** as a white solid; yield: 40 mg (63%); $[\alpha]_D^{20}$: −10.7 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.68–7.58 (m, 4H), 7.48 (d, 1H, *J* = 7.7 Hz), 7.46–7.30 (m, 6H), 5.53 (dt, 1H, *J* = 15.3 and 6.2 Hz), 5.42 (dd, 1H, *J* = 15.4 and 6.3 Hz), 4.61 (d, 1H, *J* = 6.2 Hz), 3.91 (br s, 1H), 3.87–3.74 (m, 3H), 2.73 (br s, 1H), 2.41 (d, 1H, *J* = 6.7 Hz), 1.93–1.82 (m, 2H), 1.26 (br s, 52H), 1.12 (s, 9H), 0.88 (t, 6H, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 173.2, 136.1, 135.9, 135.2, 132.9, 130.2, 130.1, 128.0, 127.7, 127.4, 75.8, 73.1, 65.3, 53.4, 34.6, 32.2, 32.1, 29.9, 29.5, 29.3, 28.9, 27.1, 25.8, 22.8, 19.4, 14.3.

(2*S*,3*S*,2′*R*,3′*E*)-2-*N*-(2′-*tert*-Butyldiphenylsilyloxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (37)

Obtained from **35** (40 mg, 0.046 mmol) following the procedure described for compound **23**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 8/2) afforded **37** as a white solid; yield: 31 mg (82%); mp 49 °C; $[\alpha]_D^{20}$: −4.1 (*c* 1.00, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.63 (ddd, 4H, *J* = 14.6, 8.0 and 1.5 Hz), 7.48–7.31 (m, 7H), 5.67 (dtd, 1H, *J* = 15.3, 6.8 and 1.0 Hz), 5.49 (dd, 1H, *J* = 15.4 and 6.0 Hz), 4.63 (d, 1H, *J* = 5.3 Hz), 3.98–3.88 (m,

1H), 3.81–3.57 (m, 3H), 2.65 (br s, 1H), 2.17 (br s, 1H), 2.00–1.87 (m, 2H), 1.76–1.58 (m, 2H), 1.25 (br s, 50H), 1.13 (s, 9H), 0.88 (t, 6H, $J=6.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=172.9$, 136.0, 135.8, 134.4, 133.1, 132.8, 130.3, 130.2, 128.0, 127.8, 127.5, 75.6, 73.1, 65.6, 52.9, 34.4, 32.3, 32.1, 30.3, 29.9, 29.8, 29.5, 29.3, 29.1, 27.1, 25.7, 22.8, 19.3, 14.3.

(2*R*,3*R*,2′*R*,3′*E*)-2-*N*-(2′-hydroxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (38)

Obtained from **36** (38 mg, 0.046 mmol) following the procedure described for compound **1**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 6/4) afforded **38** as a white solid; yield: 19 mg (70%); $[\alpha]_D^{20}$: −22.0 (*c* 0.25, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C): $\delta=6.71$ (d, 1H, $J=8.0$ Hz), 5.91 (dtd, 1H, $J=15.4$, 6.9 and 0.8 Hz), 5.58 (ddt, 1H, $J=15.5$, 7.1 and 1.4 Hz), 4.52 (d, 1H, $J=$ 7.1 Hz), 3.95 (td, 1H, $J=6.4$ and 2.0 Hz), 3.93–3.86 (m, 1H), 3.83 (d *like*, 2H, $J=4.3$ Hz), 3.06 (br s, 1H), 2.41 (br s, 1H), 2.36 (br s, 1H), 2.10 (q *like*, 2H, $J=6.8$ Hz), 1.54–1.37 (m, 6H), 1.29 (br s, 46H), 0.90 (t, 6H, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C): $\delta=173.4$, 136.4, 128.2, 73.3, 73.0, 65.2, 54.2, 34.8, 32.4, 32.1, 29.9, 29.5, 29.4, 29.2, 25.7, 22.8, 14.1.

(2*S*,3*S*,2′*R*,3′*E*)-2-*N*-(2′-hydroxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (39)

Obtained from **37** (26 mg, 0.032 mmol) following the procedure described for compound **1**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 45/55) afforded **39** as a white solidM; yield: 10 mg (56%); $[\alpha]_D^{20}$: −3.7 (*c* 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C): $\delta=6.76$ (d, 1H, $J=7.9$ Hz), 5.91 (dtd, 1H, $J=15.5$, 6.9 and 1.0 Hz), 5.59 (ddt, 1H, $J=15.3$, 7.0 and 1.4 Hz), 4.54 (d, 1H, $J=$ 7.1 Hz), 3.99–3.93 (m, 1H), 3.93–3.87 (m, 1H), 3.84 (d *like*, 2H, $J=4.2$ Hz), 2.94 (br s, 1H), 2.35 (br s, 1H), 2.28 (br s, 1H), 2.10 (q *like*, 2H, $J=6.9$ Hz), 1.53–1.37 (m, 6H), 1.29 (br s, 46H), 0.90 (t, 6H, $J=6.9$ Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C): $\delta=173.4$, 136.3, 128.1, 73.4, 73.1, 65.3, 54.2, 34.8, 32.4, 32.1, 29.9, 29.5, 29.4, 29.2, 25.8, 22.8, 14.1.

(2*R*,3*R*,2′*R*,3′*Z*)-2-*N*-(2′-Hydroxy-3′-octadecenoyl)-1,3-*O*-isopropylidene-[2-aminooctadecane-1,3-diol] (40)

Obtained from **33** (40 mg, 0.12 mmol) and **13** (42 mg, 0.10 mmol) following the procedure described for compound **21**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 8/2) afforded **40** as a white solid; yield: 52 mg (71%); mp 53 °C; $[\alpha]_D^{20}$: −75.9 (*c* 1.02, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=6.66$ (d, 1H, $J=9.5$ Hz), 5.80 (dt, 1H, $J=10.7$ and 7.6 Hz), 5.45 (dd, 1H, $J=10.8$ and 9.2 Hz), 4.89 (dd, 1H, $J=9.1$ and 2.4 Hz), 4.07 (dd, 1H, $J=$ 12.0 and 1.7 Hz), 3.99–3.90 (m, 1H), 3.84 (dd, 1H, $J=9.5$ and 1.7 Hz), 3.71 (dd, 1H, $J=12.0$ and 1.7 Hz), 3.29 (d, 1H, $J=3.3$ Hz), 2.31–2.15 (m, 2H), 1.48–1.34 (m, 4H), 1.46 (s, 3H), 1.38 (s, 3H), 1.25 (br s, 48H), 0.87 (t, 6H, $J=6.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=172.3$, 136.6, 127.6, 99.2, 71.2, 67.9, 65.0, 46.0, 32.1, 31.9, 29.8, 29.7, 29.6, 29.5, 28.1, 24.8, 22.8, 18.7, 14.3.

(2*S*,3*S*,2′*R*,3′*Z*)-2-*N*-(2′-Hydroxy-3′-octadecenoyl)-1,3-*O*-isopropylidene-[2-aminooctadecane-1,3-diol] (41)

Obtained from (*ent*)-**33** (40 mg, 0.12 mmol) and **13** (42 mg, 0.10 mmol) following the procedure described for compound **21**. Purification of the residue by flash chromatography (cyclohexane/AcOEt: 8/2) afforded **41** as a white solid; yield: 42 mg (58%); $[\alpha]_D^{20}$: −40.8 (*c* 1.03, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta=6.84$ (d, 1H, $J=9.6$ Hz), 5.80 (dt, 1H, $J=10.8$ and 7.5 Hz), 5.46 (dd, 1H, $J=10.7$ and 9.1 Hz), 4.89 (dd, 1H, $J=9.0$ and 1.9 Hz), 4.06 (dd, 1H, $J=12.0$ and 1.7 Hz), 3.99–3.88 (m, 1H), 3.82 (dd, 1H, $J=9.6$ and 1.6 Hz), 3.70 (dd, 1H, $J=12.0$ and 1.7 Hz), 3.23 (d, 1H, $J=3.0$ Hz), 2.22 (q, 2H, $J=7.2$ Hz), 1.50–1.35 (m, 4H), 1.46 (s, 3H), 1.37 (s, 3H), 1.25 (br s, 48H), 0.87 (t, 6H, $J=6.7$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta=172.4$, 136.9, 127.4, 99.2, 71.2, 68.0, 65.0, 46.0, 32.1, 29.8, 29.6, 29.5, 28.1, 24.9, 22.8, 18.7, 14.3.

(2*R*,3*R*,2′*R*,3′*Z*)-2-*N*-(2′-Hydroxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (42)

Obtained from **40** (43 mg, 0.069 mmol) following the procedure described for compound **28**. Purification of the residue by flash chromatography ($CHCl_3$/MeOH: 96/4) afforded **42** as a white solid; yield: 29 mg (72%); $[\alpha]_D^{20}$: −61.2 (*c* 0.30, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C): $\delta=6.72$ (d, 1H, $J=8.1$ Hz), 5.77 (dt, 1H, $J=10.6$ and 7.6 Hz), 5.46 (dd, 1H, $J=10.7$ and 9.0 Hz), 4.88 (d, 1H, $J=8.9$ Hz), 3.95 (td, 1H, $J=6.4$ and 2.1 Hz), 3.92–3.85 (m, 1H), 3.82 (d, 2H, $J=$ 4.4 Hz), 2.49 (br s, 2H), 2.30–2.16 (m, 2H), 1.54–1.36 (m, 4H), 1.29 (br s, 48H), 0.90 (t, 6H, $J=6.8$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C): $\delta=173.6$, 136.9, 127.6, 72.9, 68.6, 65.2, 54.3, 34.7, 32.1, 29.9, 29.8, 29.5, 28.2, 25.7, 22.8, 14.1.

(2*S*,3*S*,2′*R*,3′*Z*)-2-*N*-(2′-Hydroxy-3′-octadecenoyl)-[2-aminooctadecane-1,3-diol] (43)

Obtained from **41** (30 mg, 0.048 mmol) following the procedure described for compound **28**. Purification of the residue by flash chromatography ($CHCl_3$/MeOH: 96/4) afforded **43** as a white solid; yield: 21 mg (75%); $[\alpha]_D^{20}$: −62.2 (*c* 0.31, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C): $\delta=6.78$ (d, 1H, $J=8.1$ Hz), 5.78 (dt, 1H, $J=10.2$ and 7.4 Hz), 5.46 (dd, 1H, $J=10.6$ and 9.0 Hz), 4.89 (d, 1H, $J=8.7$ Hz), 3.95 (td, 1H, $J=5.2$ and 1.7 Hz), 3.91–3.85 (m, 1H), 3.83 (br s, 1H), 3.82 (br s, 1H), 3.06 (br s, 1H), 2.46 (br s, 1H), 2.30–2.16 (m, 2H), 1.54–1.38 (m, 4H), 1.29 (br s, 48H), 0.90 (t, 6H, $J=$ 6.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz, 50 °C): $\delta=173.6$, 137.0, 127.5, 72.9, 68.7, 65.2, 54.2, 34.7, 32.1, 29.9, 29.5, 28.2, 25.7, 22.8, 14.1.

Supporting Information

^{1}H NMR, ^{13}C NMR and mass spectra for compounds **1**, **4**, **9**–**29** and **31**–**43** as well as preliminary results for the asymmetric transfer hydrogenation of **4** are available in the Supporting Information.

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