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Tetrahedron: *Asymmetry* 15 (2004) 1899–1908

Total synthesis of sulfobacin A through dynamic kinetic resolution of a racemic β-keto-α-amino ester hydrochloride

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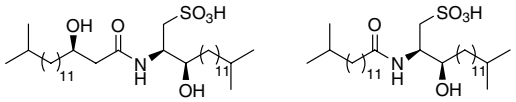
Received 25 March 2004; accepted 7 May 2004
Available online 4 June 2004

Abstract—A total synthesis of sulfobacin A, a von Willebrand factor receptor antagonist, is described. Our synthetic approach relies uniquely on catalytic asymmetric reactions for the creation of the three stereogenic centers without using chiral building blocks. The key steps of this short route to sulfobacin A involve ruthenium-mediated asymmetric hydrogenation reactions of a β-keto ester and a racemic β-keto-α-amino ester hydrochloride to afford, respectively, the corresponding enantiomerically pure β-hydroxy ester and the enantioenriched *anti* β-hydroxy α-amino ester hydrochloride through dynamic kinetic resolution.

1. Introduction

Sulfobacins A **1** and B (Scheme 1) are novel von Willebrand factor (vWF) receptor antagonists produced by *Chryseobacterium* sp. NR 2993. They were isolated by Kamiyama et al.[1] in 1995 from a soil sample collected in Iriomote Island. The same year, Kobayashi et al.[2] also isolated sulfobacin A **1** from *Flavobacterium* sp., separated from the marine bivalve *Cristaria plicata* collected in Ishikary Bay.



Scheme 1. Structures of sulfobacins A and B.

Sulfobacins A and B showed potent inhibitory activity against the binding of vWF to its receptor in a competitive manner with IC_{50} of 0.47 μM for sulfobacin A and 2.2 μM for sulfobacin B.[1] These compounds also exhibit inhibitory activity against DNA polymerase α.[2]

Two total syntheses of sulfobacin A **1** were reported in 1998 by the groups of Shioiri[3] and Mori.[4] Their approaches involved either a chiral building block or a chiral auxiliary to set one or two of the three stereogenic centers present in the natural product. We have also recently achieved an efficient total synthesis of this compound via sequential catalytic asymmetric hydrogenation and diastereoselective electrophilic amination.[5] We report herein an improved synthesis of sulfobacin A **1** by using uniquely catalytic asymmetric reactions for the highly diastereo- and enantioselective construction of the three stereogenic centers.

It has been established in previous work[6] that dynamic kinetic resolution of β-keto α-amido ester using ruthenium-catalyzed hydrogenation allows the efficient preparation of *syn*-β-hydroxy-α-amino acids with excellent diastereo- and enantioselectivities.[7] We have recently disclosed that highly stereoselective synthesis of *anti*-β-hydroxy-α-amino ester hydrochlorides can be directly achieved from the racemic β-keto-α-amino ester hydrochlorides by asymmetric hydrogenation with chiral ruthenium complexes through dynamic kinetic resolution.[8,9]

Herein as an extension of this work, and in connection with our ongoing program directed towards the total synthesis of biologically relevant natural products,[10] the application of this methodology to the total synthesis of sulfobacin A is described.

Our retrosynthetic analysis for sulfobacin A **1** involves disconnection of the amide bond into β-hydroxy acid **7**

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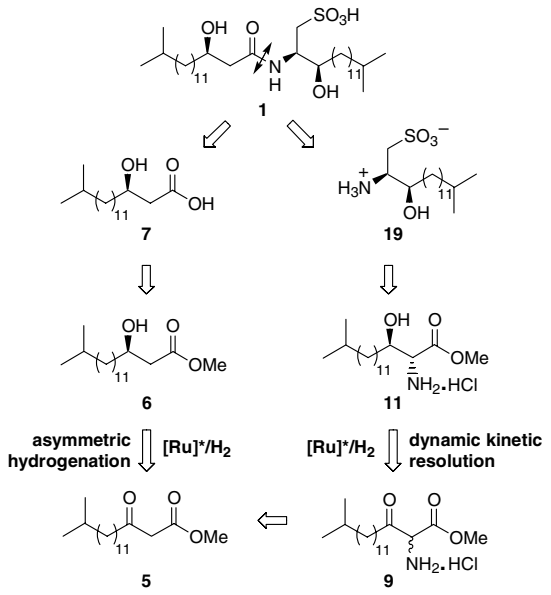
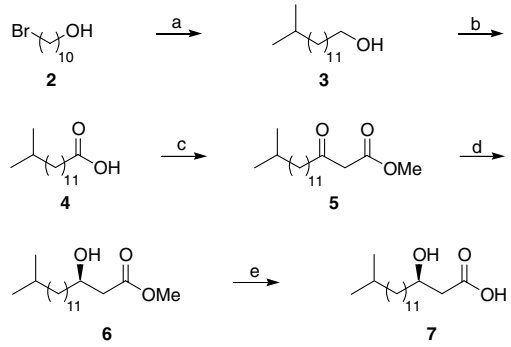
doi:10.1016/j.tetasy.2004.05.004

and aminosulfonic acid **19** (Scheme 2). Thus, compound **19** would result from the *anti*-β-hydroxy-α-amino ester hydrochloride **11**, which could be obtained by asymmetric hydrogenation of racemic β-keto-α-amino ester hydrochloride **9** through dynamic kinetic resolution. β-Keto ester **5** would serve both for the preparation of compound **9** and for the synthesis of β-hydroxy acid **7** by ruthenium-mediated asymmetric hydrogenation followed by simple alkaline treatment.



Scheme 2. Retrosynthetic analysis for sulfobacin A **1**.

The synthesis of the required β-hydroxy acid **7** began with the commercially available 10-bromodecan-1-ol **2**, which was converted into alcohol **3** by treatment with isoamylmagnesium bromide in the presence of dilithium tetrachlorocuprate[4b] (Scheme 3). After oxidation with Jones' reagent to the corresponding carboxylic acid **4**, homologation to β-keto ester **5** was performed using Masamune's procedure.[11] Thus, the addition of carbonyl diimidazole to **4** followed by treatment with the magnesium salt of monomethyl malonic acid afforded β-keto ester **5** in 81% yield.

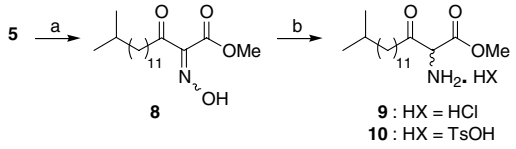


Scheme 3. Reagents and conditions: (a) $Me_2CH(CH_2)_2MgBr$, Li_2CuCl_4, THF, −78 °C to rt, 12 h, 95%; (b) Jones' reagent, acetone, rt, 1 h, 88%; (c) carbonyl diimidazole, THF, rt, 6 h then $Mg(O_2CCH_2CO_2Me)_2$, THF, rt, 16 h, 81%; (d) H_2 (6 bar), $RuCl_3$/(*R*)-MeO-BIPHEP (1 mol%), MeOH, 80 °C, 23 h, 96%, ee >99%; (e) 1 N NaOH, MeOH, 0 °C, 30 min, then rt, 3 h, 89%.

For the asymmetric hydrogenation of **5**, we used our recently reported simple procedure for the in situ preparation of chiral ruthenium catalysts[12] starting directly from anhydrous ruthenium trichloride.

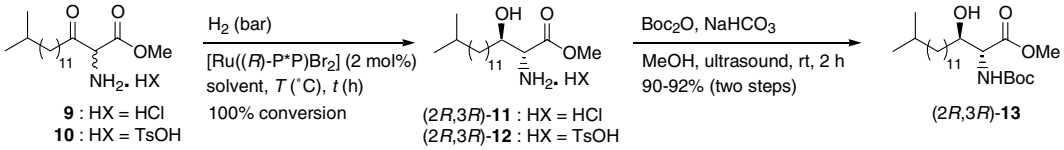
Thus, hydrogenation of **5** was carried out in methanol at 80 °C under a low pressure of hydrogen (6 bar), using 1 mol% of the $RuCl_3$/(*R*)-MeO-BIPHEP system. Under these conditions, β-hydroxy ester **6** was obtained in 96% yield and with excellent enantiomeric excess (ee >99%, determined by chiral HPLC analysis), $[\alpha]_D^{25} = -14.3$ (*c* 0.51, $CHCl_3$), lit.[1b] $[\alpha]_D^{20} = -12.7$ (*c* 0.52, $CHCl_3$). Finally, alkaline treatment of **6** furnished β-hydroxy carboxylic acid **7**, $[\alpha]_D^{25} = -11.6$ (*c* 1.0, $CHCl_3$), lit.[13] $[\alpha]_D^{20} = -12.0$ (*c* 1.0, $CHCl_3$), required for the final coupling reaction with aminosulfonic acid **19**.

The synthesis of **19** also involved β-keto ester **5**, which was first converted into β-keto α-amino ester hydrochloride **9** via a two-step sequence (Scheme 4). Thus, reaction of **5** with butyl nitrite in the presence of sulfuric acid afforded the corresponding oxime **8** and subsequent hydrogenation with Pd/C in a solution of HCl/MeOH then provided quantitatively the β-keto α-amino ester hydrochloride **9** required for the dynamic kinetic resolution. To study the influence of the counter ion of the ammonium salt on the reaction, we also prepared the parent compound *p*-toluenesulfonic acid salt **10** by hydrogenation of **8** with Pd/C in the presence of a stoichiometric amount of *p*-toluenesulfonic acid. The dynamic kinetic resolution of these compounds was then studied using as a ligand either (*R*)-MeO-BIPHEP or (*R*)-SYNPHOS,[14] a new atropisomeric ligand bearing a benzodioxane core synthesized in our group (Scheme 5, Table 1).



Scheme 4. Reagents and conditions: (a) BuONO, conc. H_2SO_4, Et_2O, 0 °C, 45 min then rt, 1.5 h, 98%; (b) for **9**, H_2 (1 atm), Pd/C 5%, HCl/MeOH, quant.; for **10**, H_2 (1 atm), Pd/C 5%, MeOH, PTSA, quant.

The asymmetric hydrogenation of **9** was first conducted in methanol at 50 °C under 20 bar of hydrogen using 2 mol% of the [Ru((*R*)-MeO-BIPHEP)Br_2] complex, generated in situ according to our convenient procedure[15] from commercially available (COD)Ru(2-methylallyl)$_2$. Under these conditions, (2*R*,3*R*)-**11** was obtained with excellent diastereoselectivity while moderate enantioselectivity was observed for the *anti* product (de = 96%, ee = 41%, entry 1). The de and ee were measured by chiral HPLC after conversion of the hydrogenated product into the corresponding carbamate **13**, which will serve as well for the end of the synthesis of sulfobacin A.



Scheme 5.

Table 1. Dynamic kinetic resolution of racemic **9** and **10** by using ruthenium-catalyzed asymmetric hydrogenation[a]

Entry	HX	Ligand	Solvent	P (bar)	T (°C)	t (h)	d.r. *anti*/*syn*[b]	Ee[b,c] (%)
1	HCl	(*R*)-MeO-BIPHEP	MeOH	20	50	72	98/2	41
2	HCl	(*R*)-MeO-BIPHEP	MeOH	80	50	48	97/3	35
3	HCl	(*R*)-MeO-BIPHEP	CH_2Cl_2	20	50	72	90/10	85
4	HCl	(*R*)-SYNPHOS	CH_2Cl_2	130	50	96	90/10	88
5	HCl	(*R*)-MeO-BIPHEP	CH_2Cl_2/MeOH (10/1)	70	50	72	91/9	88
6	HCl	(*R*)-SYNPHOS	CH_2Cl_2/MeOH (10/1)	12	50	30	96/4	92
7	HCl	(*S*)-SYNPHOS	CH_2Cl_2/MeOH (10/1)	12	50	30	96/4[d]	92
8	TsOH	(*R*)-MeO-BIPHEP	CH_2Cl_2/MeOH (10/1)	70	50	72	92/8	84
9	TsOH	(*R*)-MeO-BIPHEP	CH_2Cl_2/MeOH (10/1)	12	50	72	93/7	82
10	TsOH	(*R*)-SYNPHOS	CH_2Cl_2/MeOH (10/1)	12	50	72	93/7	83

[a] Complete conversions were observed for the asymmetric hydrogenation in all cases and were determined by ^{1}H NMR analysis of the crude reaction mixture.

[b] The diastereo- and enantiomeric excesses were determined by chiral HPLC after conversion of **11** and **12** into the corresponding carbamate **13**: Chiralcel OD-H column; eluent, hexane/propan-2-ol: 99/1; flow rate: 1.0 mL/min; UV detection: 215 nm; t_R 17.93 min, (2*S*,3*S*)-**13** isomer; t_R 19.21 min, (2*S*,3*R*)-**13** isomer; t_R 20.15 min, (2*R*,3*S*)-**13** isomer; t_R 21.17 min, (2*R*,3*R*)-**13** isomer.

[c] The enantiomeric excess was measured for the *anti*-β-hydroxy-α-amino ester **13**.

[d] The (2*S*,3*S*)-**11** isomer was the major product in this case.

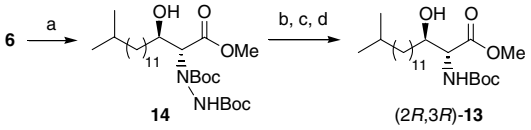
Increasing the hydrogen pressure to 80 bar resulted in a slight decrease of both diastereo- and enantioselectivities (de = 94%, ee = 35%, entry 2). Interestingly, when using dichloromethane in place of methanol, the ee raised to 85% while the de remained correct (de = 80%, ee = 85%, entry 3). Similar results were obtained using (*R*)-SYNPHOS at higher pressure (130 bar) instead of (*R*)-MeO-BIPHEP (de = 80%, ee = 88%, entry 4).

When the reaction was carried out in a mixture of dichloromethane/methanol (10/1), both de and ee were still high (de = 82%, ee = 88%, entry 5). The best results were obtained when using 2 mol% of [Ru((*R*)-SYNPHOS)Br_2] in dichloromethane/methanol (10/1) at 50 °C under 12 bar of hydrogen.

Under these conditions, *anti*-(2*R*,3*R*)-**11** was obtained with a high level of diastereo- and enantioselectivity (de = 92%, ee = 92%, entry 6). For analytical purposes, the (2*S*,3*S*)-**11** isomer has been prepared as well using the other configuration of the chiral diphosphine (de = 92%, ee = 92%, entry 7).

We have then studied the dynamic kinetic resolution of the *p*-toluenesulfonic acid salt **10** to investigate the effect of the counter ion of the ammonium salt. The hydrogenation reaction was first performed at 50 °C in dichloromethane/methanol (10/1) under 70 bar of hydrogen with (*R*)-MeO-BIPHEP and afforded (2*R*,3*R*)-**12** with 84% de and 84% ee, comparable to the results obtained previously for compound **9** under the same conditions (entry 8 vs entry 5). Decreasing the hydrogen pressure to 12 bar resulted in similar diastereo- and enantioselectivities (de = 86%, ee = 82–83%, entries 9 and 10). Nevertheless the de and ee with the *p*-toluenesulfonic acid salt **10** remained inferior to the best results obtained with hydrochloride compound **9** (entry 10 vs entry 6).

The absolute configuration of β-hydroxy α-amino ester **13** was unambiguously established by comparison with an authentic sample of *anti*-(2*R*,3*R*)-**13** prepared during our former total synthesis of sulfobacin A[5] by sequential catalytic hydrogenation and diastereoselective electrophilic amination (Scheme 6).

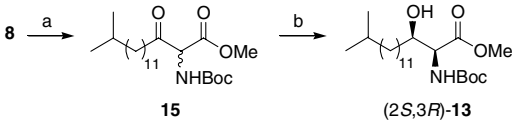


Scheme 6. Reagents and conditions: (a) MeZnBr (1 equiv), 0 °C, 1 h; LDA (2 equiv), −78 °C, 1 h; DTBAD (2 equiv), −78 °C, 2 h, 72%, de >95%; (b) TFA, CH_2Cl_2, rt, 3 h; (c) H_2 (1 atm), Raney Ni, MeOH, ultrasound, rt, 14 h; (d) Boc_2O, $NaHCO_3$, MeOH, ultrasound, rt, 3.5 h, 80% from **14**.

The *anti*-*N*,*N*′-Boc-α-hydrazino-β-hydroxy ester **14** was readily obtained from enantiomerically pure β-hydroxy ester **6** by electrophilic amination with di-*tert*-butylazodicarboxylate (DTBAD).[16] Thus, treatment of **6** with methylzinc bromide followed by lithium diisopropylamide at −78 °C furnished the resulting zinc enolate, which was reacted with DTBAD to afford **14** in 72% yield as a single diastereomer after separation by flash chromatography (de >95%, determined by ^{1}H NMR). Deprotection of the hydrazine function followed by

cleavage of the N–N bond by hydrogenolysis with Raney nickel under ultrasound,[18] and subsequent protection of the resulting amine with di-*tert*-butyl dicarbonate under ultrasound[18] finally afforded (2*R*,3*R*)-**13** (de = 96%, ee = 99%, chiral HPLC) in 80% overall yield starting from **14**.

Authentic samples of both enantiomers of *syn*-β-hydroxy-α-amino ester (2*S*,3*R*)-**13** and (2*R*,3*S*)-**13** were also readily obtained through dynamic kinetic resolution of racemic β-keto-α-amino ester **15** using either (*R*)- or (*S*)-MeO-BIPHEP as a ligand (Scheme 7).



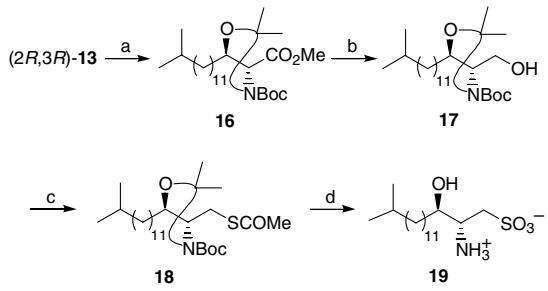
Scheme 7. Reagents and conditions: (a) Zn, AcOH, Boc_2O, Δ, 3 h then rt, 1.5 h, 82%; (b) for (2*S*,3*R*)-**13**, H_2 (120 bar), [Ru((*R*)-MeO-BIPHEP)Br_2] (1 mol%), CH_2Cl_2, 50 °C, 96 h, 94%, ee = 94%, de = 90%; for (2*R*,3*S*)-**13**, H_2 (120 bar), [Ru((*S*)-MeO-BIPHEP)Br_2] (1 mol%), CH_2Cl_2, 50 °C, 96 h, 90%, ee = 94%, de = 90%.

Compound **15** was first prepared by reduction of oxime **8** with zinc in acetic acid in the presence of di-*tert*-butyl dicarbonate. Subsequent hydrogenation of **15** using 1 mol% of [Ru((*R*)-MeO-BIPHEP)Br_2] in CH_2Cl_2 at 50 °C under 120 bar of hydrogen delivered *syn*-(2*S*,3*R*)-**13** with high diastereo- and enantiomeric excesses (de = 90%, ee = 94%). The (2*R*,3*S*)-**13** isomer was also prepared under similar conditions using (*S*)-MeO-BIPHEP as a ligand (de = 90%, ee = 94%).

It should be pointed out that our approach should allow an easy access to all eight stereoisomers of sulfobacin A since both β-hydroxy acids (*R*)-**7** and (*S*)-**7** can be readily obtained using the appropriate configuration of the chiral ligand during the asymmetric hydrogenation step of compound **5**, and both enantiomers of *syn*- and *anti*-β-hydroxy-α-amino ester **13** can be prepared via dynamic kinetic resolution of either β-keto-α-amino ester hydrochloride **9** or β-keto α-Boc-amino ester **15** using (*R*) or (*S*) chiral diphosphine.

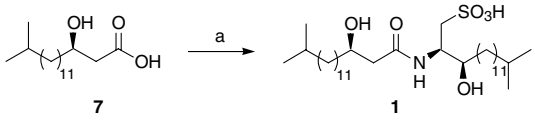
Completion of the synthesis of sulfobacin A then required protection of compound (2*R*,3*R*)-**13** (Scheme 8). Thus, treatment of (2*R*,3*R*)-**13** with 2,2-dimethoxypropane with a catalytic amount of $BF_3{\cdot}Et_2O$ afforded the corresponding oxazolidine **16**, which was subsequently reduced to the primary alcohol **17** by using calcium borohydride. After conversion of **17** into the corresponding mesylate, all attempts to perform nucleophilic substitution with sodium sulfite failed to afford the expected sulfonic acid. Finally, Mitsunobu[19] reaction of **17** with thioacetic acid furnished thioester **18** in 95% yield and subsequent oxidation with hydrogen peroxide in trifluoroacetic acid led to the target compound **19**.

The final coupling reaction of **19** with carboxylic acid **7** was carried out using HONB and DCC to form the corresponding active ester of **7**, which was reacted with



Scheme 8. Reagents and conditions: (a) $Me_2C(OMe)_2$, $BF_3{\cdot}Et_2O$, CH_2Cl_2, rt, 1 h, 93%; (b) $Ca(BH_4)_2$, THF/EtOH, −15 °C to rt, 22 h, 94%; (c) CH_3COSH, *i*PrOCON=NCO_2*i*Pr, PPh_3, THF, 0 °C, 1 h, then rt, 16 h, 95%; (d) H_2O_2, TFA, rt, 1 h.

the sodium salt of **19** in a mixture of dioxane and water at room temperature (Scheme 9).[20] After treatment with Amberlite IR-120B (H^+ form), sulfobacin A **1** was obtained in 20% yield from **18** and spectral data of **1** were found to be in agreement with reported literature data.[1b,3b,4a]



Scheme 9. Reagents and conditions: (a) HONB, DCC, THF/dioxane, 0 °C, 40 min, rt, 24 h then **19**, $NaHCO_3$, dioxane/H_2O, rt, 20 h, 20% from **18**.

In summary, in spite of the moderate yield obtained in the final coupling reaction between compounds **7** and **19**, our route to sulfobacin A is a very short one (14 steps) and compares favorably with the other reported syntheses (Shiori:[3] 21 steps, Mori:[4] 24 steps). The ruthenium-catalyzed asymmetric hydrogenation of β-keto ester **5** and the dynamic kinetic resolution of β-keto-α-amino ester hydrochloride **9** allowed the highly stereocontrolled construction of the three stereogenic centers only through catalytic asymmetric reactions without using either chiral auxiliaries or chiral building blocks. Moreover, by choosing either the (*R*) or (*S*) configuration of the chiral ligand for the asymmetric hydrogenation of compounds **5**, **9** or **15**, this flexible approach should allow the easy preparation of all eight isomers of sulfobacin A for structure–activity relationship studies.

2. Experimental

All solvents were reagent grade and distilled under argon prior to use. Amines were distilled from potassium hydroxide and CH_2Cl_2 from calcium hydride. THF and Et_2O were distilled from sodium benzophenone. Unless special mention, all reactions were carried out under an argon atmosphere. All commercially available reagents were used without further purification unless otherwise indicated. Nuclear magnetic resonance: ^1H and ^{13}C NMR spectra were recorded either at 200 and 50 MHz,

respectively, on an AC200 Bruker spectrometer, or at 300 and 75 MHz, respectively, on an Avance 300 Bruker spectrometer, or at 400 and 100 MHz, respectively, on an Avance 400 Bruker spectrometer. Chemical shifts are given in ppm referenced to the residual proton resonance of the solvent (7.26 ppm for $CDCl_3$) for ^1H NMR. For ^{13}C NMR, chemical shifts are referenced to the central peak of the solvent (77.1 ppm for $CDCl_3$). Coupling constants (J) are given in hertz (Hz). Infrared spectra (IR) were recorded on either a Perkin–Elmer 783G spectrometer or an IRFT Nicolet 210 spectrometer. Mass spectra (MS) were measured on a Nermag R10-10C mass spectrometer (DCI/NH_3) and on a PE Sciex API 3000 mass spectrometer (ESI). Flash column chromatography was performed on Merck silica gel (0.040–0.063 mesh). Thin layer chromatography (TLC) analysis was performed on Merck silica gel 60 PF 254 and revealed with either an ultra-violet lamp ($\lambda = 254$ nm) or a potassium permanganate solution. Specific rotation values were recorded on a Perkin–Elmer 241 polarimeter. HPLC analyses were performed on a Waters 600 system with a Chiralcel OD-H column.

2.1. 13-Methyl-tetradecan-1-ol 3[4b]

To a stirred solution of 10-bromo-decan-1-ol **2** (5.0 g, 21.1 mmol) in THF (50 mL) at −78 °C was added dropwise a solution of $(Me)_2CH(CH_2)_2MgBr$ in THF (80.7 mL, 0.98 M, 78.1 mmol) followed by a solution of Li_2CuCl_4 in THF (2.5 mL, 0.1 M, 0.25 mmol). The reaction mixture was allowed to warm to room temperature with stirring overnight, then quenched with saturated aqueous NH_4Cl and extracted with ethyl acetate. The combined organic layers were washed with water, saturated aqueous $NaHCO_3$, and brine, then dried over $MgSO_4$ and concentrated. Purification of the residue by flash chromatography afforded pure 13-methyl-tetradecan-1-ol **3** (4.56 g, 95%) as a colorless oil. R_f 0.21 (cyclohexane/ethyl acetate: 8/2). IR (film): 3392, 2926, 2854 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, 6H, $J = 6.6$ Hz), 1.16 (m, 2H), 1.26 (br s, 18H), 1.44–1.60 (m, 4H), 3.63 (t, 2H, $J = 6.6$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5, 25.6, 27.3, 27.9, 29.3, 29.5, 29.6, 29.8, 32.7, 39.0, 62.9. MS (DCI/NH_3): $m/z = 246$ $[M+NH_4]^+$.

2.2. 13-Methyl-tetradecanoic acid 4

To a solution of 13-methyl-tetradecan-1-ol **3** (42.2 g, 184.8 mmol) in acetone (750 mL) was added dropwise at 0 °C Jones' reagent [prepared by adding at 0 °C conc. H_2SO_4 (21 mL) to a solution of CrO_3 (33.9 g, 339.0 mmol) in water (145 mL)]. After stirring at room temperature for 1 h, the reaction mixture was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate: 8/2) afforded pure 13-methyl-tetradecanoic acid **4** (39.4 g, 88%) as a white solid, mp 47–49 °C, lit.[21] 46.5–47 °C. R_f 0.28 (cyclohexane/ethyl acetate: 8/2). IR (KBr): 3416, 2950, 2919, 2850, 1701 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, 6H, $J = 6.6$ Hz), 1.17 (m, 2H), 1.25 (br s, 16H), 1.45–1.69 (m, 3H), 2.35 (t, 2H, $J = 7.4$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.6, 24.6, 26.8, 27.3, 27.9, 29.0, 29.1, 29.3, 29.5, 29.8, 34.0, 39.0, 180.3. MS (DCI/NH_3): $m/z = 260$ $[M+NH_4]^+$. Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.32; H, 12.47. Found: C, 74.33; H, 12.56.

2.3. Methyl 15-methyl-3-oxo-hexadecanoate 5

To a solution of methyl hydrogen malonate (21.6 g, 183 mmol) in THF (140 mL) was added magnesium ethoxide (10.5 g, 91.5 mmol). The mixture was stirred at room temperature for 1 h and concentrated to afford the magnesium salt of methyl malonic acid as a yellow solid, which was used for the next reaction without purification. To a solution of carboxylic acid **4** (11.4 g, 47.1 mmol) in THF (250 mL) was added carbonyl diimidazole (9.2 g, 57.0 mmol) and the mixture was stirred at room temperature for 6 h. This solution was then added to the previously prepared magnesium salt (14.9 g, 57.7 mmol). The reaction mixture was stirred for 20 h at 25 °C and concentrated. The residue was dissolved in Et_2O (300 mL) and acidified with HCl 1 M. After the layers were separated, the aqueous phase was extracted with Et_2O and the combined organic layers were washed with water and saturated aqueous $NaHCO_3$, dried with $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate: 95/5) afforded **5** (11.5 g, 81%) as a white solid, mp 44–45 °C. R_f 0.32 (cyclohexane/ethyl acetate: 9/1). IR (KBr): 2950, 2914, 2842, 1747, 1711 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, 6H, $J = 6.6$ Hz), 1.16 (m, 2H), 1.25 (br s, 16H), 1.30–1.70 (m, 3H), 2.52 (t, 2H, $J = 7.3$ Hz), 3.44 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.3, 23.1, 27.1, 27.6, 28.7, 29.0, 29.1, 29.3, 29.6, 38.7, 42.7, 50.7, 52.0, 167.4, 202.5. MS (DCI/NH_3): $m/z = 299$ $[M+H]^+$, 316 $[M+NH_4]^+$. Anal. Calcd for $C_{18}H_{34}O_3$: C, 72.44; H, 11.48. Found: C, 72.30; H, 11.53.

2.4. Methyl (*R*)-3-hydroxy-15-methyl-hexadecanoate 6

(*R*)-MeO-BIPHEP (93.8 mg, 0.16 mmol) and anhydrous $RuCl_3$ (33.3 mg, 0.16 mmol, purchased from Aldrich Chemicals) were placed in a round-bottomed tube and degassed by three vacuum/argon cycles at room temperature. β-Keto ester **5** (4.79 g, 16.1 mmol) was added followed by degassed methanol (15 mL). The reaction vessel was placed in a stainless steel autoclave, which was purged with hydrogen and pressurized under 6 bar. The autoclave was heated to 80 °C by circulating thermostated water in the double wall and magnetic stirring was started as soon as the required temperature was reached. After stirring for 23 h, the autoclave was cooled to room temperature, hydrogen was vented and the reaction mixture was concentrated in vacuo. Flash chromatography on silica gel (cyclohexane/ethyl acetate: 8/2) afforded β-hydroxy ester **6** (4.66 g, 96%) as a white solid, mp 32–34 °C (lit.,[1b] colorless oil). R_f 0.41 (cyclohexane/ethyl acetate: 7/3). $[\alpha]_D^{25} = -14.3$ (c 0.51, $CHCl_3$),

lit.[1b] $[\alpha]_D^{20} = -12.7$ (*c* 0.518, $CHCl_3$). IR (KBr): 3570, 3416, 2960, 2925, 2847, 1726 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, 6H, $J = 6.6$ Hz), 1.16 (m, 2H), 1.25 (br s, 18H), 1.30–1.65 (m, 3H), 2.42 (dd, 1H, $J = 16.5$ and 8.6 Hz), 2.54 (dd, 1H, $J = 16.5$ and 3.5 Hz), 2.89 (d, 1H, $J = 4.0$ Hz, OH), 3.71 (s, 3H), 3.99 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5, 25.4, 27.3, 27.9, 29.5, 29.6, 29.8, 36.4, 38.9, 41.0, 51.6, 67.9, 173.4. MS (DCI/NH_3): $m/z = 301$ $[M+H]^+$, 318 $[M+NH_4]^+$. Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 71.76; H, 12.15. HPLC analysis: column, Chiralcel OD-H; eluent, hexane/propan-2-ol: 99/1; flow rate, 1.0 mL/min; UV detection, 215 nm; t_R: 8.52 min, (*R*)-**6** isomer; t_R: 10.99 min, (*S*)-**6** isomer; ee >99%.

2.5. (*R*)-3-Hydroxy-15-methyl-hexadecanoic acid 7

To a solution of methyl (*R*)-3-hydroxy-15-methyl-hexadecanoate **6** (454 mg, 1.5 mmol) in methanol (2 mL) at 0 °C was added dropwise a 1 N aqueous solution of NaOH (4 mL). The reaction mixture was stirred at 0 °C for 0.5 h, then 3 h at room temperature, and concentrated in vacuo. The residue was acidified with 0.1 M aqueous HCl and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, concentrated, and recrystallization in cyclohexane afforded pure (*R*)-3-hydroxy-15-methyl-hexadecanoic acid **7** (385 mg, 89%) as colorless crystals, mp 55–56 °C, lit.[4b] 55–57 °C. R_f 0.27 (cyclohexane/ethyl acetate: 8/2). $[\alpha]_D^{25} = -11.6$ (*c* 1.00, $CHCl_3$), lit.[4b] $[\alpha]_D^{23} = -12.7$ (*c* 1.02, $CHCl_3$), lit.[13] $[\alpha]_D^{20} = -12.0$ (*c* 1.0, $CHCl_3$). IR (KBr): 3232, 2919, 2845, 1711 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (d, 6H, $J = 6.6$ Hz), 1.16 (m, 2H), 1.25 (br s, 18H), 1.30–1.65 (m, 3H), 2.45 (dd, 1H, $J = 16.6$ and 8.5 Hz), 2.58 (dd, 1H, $J = 16.6$ and 3.6 Hz), 4.03 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5, 25.4, 27.3, 27.9, 29.5, 29.6, 29.8, 36.4, 39.0, 41.0, 68.0. MS (DCI/NH_3): $m/z = 304$ $[M+NH_4]^+$.

2.6. Methyl 2-hydroxyimino-15-methyl-3-oxo-hexadecanoate 8

Butyl nitrite (8.8 mL, 75.2 mmol,) was added at room temperature to a solution of β-keto ester **5** (11.2 g, 37.6 mmol) in Et_2O (200 mL). After cooling to 0 °C, conc. H_2SO_4 (4 mL, 75.2 mmol) was added dropwise and the mixture was stirred 45 min at 0 °C and 1.5 h at room temperature. The reaction mixture was diluted with water and extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography on silica gel (cyclohexane/ethyl acetate: 85/15 to 8/2) afforded oxime **8** (12.0 g, 98%) as a pale yellow solid, mp 38–39 °C. R_f 0.24 and 0.36 for oximes *Z* and *E* (cyclohexane/ethyl acetate: 8/2). IR (KBr): 2919, 2854, 1746, 1714, 1691 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 6H, $J = 6.6$ Hz), 1.15 (m, 2H), 1.24 (br s, 18H), 1.58 (hept, 1H, $J = 6.6$ Hz), 1.62 (m, 2H), 2.73 (t, 2H, $J = 7.5$ Hz, minor isomer), 2.78 (t, 2H, $J = 7.5$ Hz, major isomer), 3.88 (s, 3H, minor isomer), 3.90 (s, 3H, major isomer), 9.38 (br s, 1H, OH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 23.8, 27.5, 28.0, 29.0, 29.2, 29.4, 29.5, 29.7, 29.8, 30.0, 37.9, 39.1, 52.9, 150.7, 162.2, 196.3. MS (DCI/NH_3): $m/z = 345$ $[M+NH_4]^+$. Anal. Calcd for $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16; N, 4.28. Found: C, 65.87; H, 10.24; N, 4.29.

2.7. Methyl 2-amino-15-methyl-3-oxo-hexadecanoate, hydrochloride 9

To a solution of oxime **8** (3.0 g, 9.16 mmol) in degassed methanol (45 mL) was added Pd/C 5% (317 mg, 0.15 mmol) and a degassed solution of HCl/MeOH (3 N, 10 mL). The resulting mixture was purged three times with hydrogen and stirred at room temperature for 24 h under atmospheric pressure of hydrogen. The reaction mixture was then filtered on Celite, rinsed with MeOH, and concentrated. The crude gum was dissolved in CH_2Cl_2 and concentrated to afford **9** (3.2 g, 100%) as a white solid, mp 86–89 °C. IR (KBr): 2919, 2853, 1752, 1721 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 0.86 (d, 6H, $J = 6.6$ Hz), 1.17 (m, 2H), 1.30 (br s, 18H), 1.51 (hept, 1H, $J = 6.6$ Hz), 1.62 (m, 2H), 2.77 (dt, 1H, $J = 18.3$ and 7.1 Hz), 2.90 (dt, 1H, $J = 18.3$ and 7.3 Hz), 3.89 (s, 3H). ^{13}C NMR (75 MHz, CD_3OD) δ 23.1, 24.2, 28.6, 29.2, 30.0, 30.5, 30.6, 30.7, 30.8, 30.9, 31.1, 40.3, 41.4, 54.6, 165.3, 199.5. ESI MS: $m/z = 314$ $[M-HCl+H]^+$, 336 $[M-HCl+Na]^+$.

2.8. Methyl 2-amino-15-methyl-3-oxo-hexadecanoate, PTSA salt 10

To a solution of oxime **8** (1.50 g, 4.58 mmol) in degassed methanol (20 mL) was added Pd/C 5% (159 mg, 0.075 mmol) and *p*-toluenesulfonic acid (0.87 g, 4.58 mmol). The resulting mixture was purged three times with hydrogen, pressurized under 1 bar and stirred for 20 h at room temperature. The reaction mixture was then filtered on Celite, rinsed with MeOH, and concentrated to afford **10** (2.22 g, 100%) as a white solid, mp 127–130 °C. IR (KBr): 2924, 2848, 1757, 1721 cm^{-1}. ^1H NMR (300 MHz, CD_3OD) δ 0.88 (d, 6H, $J = 6.6$ Hz), 1.19 (m, 2H), 1.30 (br s, 18H), 1.53 (hept, 1H, $J = 6.6$ Hz), 1.60 (m, 2H), 2.37 (s, 3H), 2.74 (dt, 1H, $J = 18.3$ and 7.2 Hz), 2.89 (dt, 1H, $J = 18.3$ and 7.3 Hz), 3.89 (s, 3H), 7.24 (d, 2H, $J = 8.3$ Hz), 7.70 (d, 2H, $J = 8.3$ Hz). ^{13}C NMR (75 MHz, CD_3OD) δ 21.4, 23.1, 24.2, 28.6, 29.2, 30.0, 30.5, 30.6, 30.7, 30.8, 30.9, 31.1, 40.3, 41.4, 54.5, 127.0, 129.8, 141.7, 143.4, 165.3, 199.5. ESI MS: $m/z = 314$ $[M-TsOH+H]^+$, 336 $[M-TsOH+Na]^+$.

2.9. General procedure for the preparation of compounds (2*R*,3*R*)-11 and (2*R*,3*R*)-12 by asymmetric hydrogenation of compounds 9 and 10, respectively

Either (*R*)-MeO-BIPHEP (7.0 mg, 0.012 mmol) or (*R*)-SYNPHOS (7.7 mg, 0.012 mmol) and (COD)Ru(2-methylallyl)$_2$ (3.2 mg, 0.01 mmol, commercially available from Acros) were placed in a round-bottomed tube, degassed by three vacuum/argon cycles at room temperature, and dissolved in degassed acetone (1.5 mL). To

this suspension was added at room temperature a 0.15 N methanolic hydrobromic acid solution (147 μL, 0.022 mmol) and the mixture was stirred at 25 °C for 30 min. After evaporation of the solvent under vacuum, β-keto-α-amino esters **9** (175.0 mg, 0.5 mmol) or **10** (242.8 mg, 0.5 mmol) was added to the ruthenium complex followed by degassed CH_2Cl_2 (2 mL) and MeOH (0.2 mL). The reaction vessel was placed in a stainless steel autoclave, which was purged with hydrogen and pressurized to 12 bar. The autoclave was heated to 50 °C by circulating thermostated water in the double wall and magnetic stirring was started as soon as the required temperature was reached. After stirring for 30 h, the autoclave was cooled to room temperature, hydrogen was vented, and the reaction mixture was concentrated in vacuo to afford quantitatively β-keto α-amino esters (2*R*,3*R*)-**11** or (2*R*,3*R*)-**12**, which were used in the next step without further purification.

2.10. Methyl (2*R*,3*R*)-2-(*N*,*N*′-di-*tert*-butoxycarbonyl-hydrazino)-3-hydroxy-15-methyl-hexadecanoate (2*R*,3*R*)-14

To a cooled (0 °C) solution of MeZnBr (11.0 mmol) in THF (13 mL) prepared at room temperature from $ZnBr_2$ (2.47 g, 11.0 mmol) and MeLi (7.42 mL, 1.48 M in Et_2O, 11.0 mmol), was added a solution of β-hydroxy ester **6** (3.0 g, 10.0 mmol) in THF (12 mL). The reaction mixture was stirred at 0 °C for 1 h then cooled to −78 °C and a solution of lithium diisopropylamide (22.0 mmol) in THF (24 mL) was added dropwise. After a further 1 h at −78 °C, a solution of DTBAD (4.6 g, 20.0 mmol) in THF (12 mL) was added dropwise, the reaction mixture was stirred for 2 h then quenched at −78 °C with saturated aqueous NH_4Cl (15 mL). After extraction with Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate: 8/2) afforded *anti*-*N*,*N*′-Boc-α-hydrazino-β-hydroxy ester **14** (3.83 g, 72%) as a pale yellow solid, mp 88–89 °C. R_f 0.21 (cyclohexane/ethyl acetate: 8/2). $[\alpha]_D^{25} = -8.0$ (*c* 1.01, $CHCl_3$). IR (KBr): 3560, 3478, 3416, 3232, 2925, 1752, 1716, 1634, 1619 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ 0.88 (d, 6H, $J = 6.6$ Hz), 1.19 (m, 2H), 1.28 (br s, 18H), 1.38–1.60 (m, 3H), 1.47 (s, 9H), 1.49 (s, 9H), 3.11 (s, 1H, OH), 3.76 (s, 3H), 4.08 (m, 1H), 4.83 (m, 1H), 6.50 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, 50 °C) δ 22.6, 26.3, 27.4, 28.0, 28.2, 29.5, 29.6, 30.0, 33.8, 39.1, 52.0, 71.0, 81.9, 82.5, 155.1, 156.0, 170.7. MS (DCI/NH_3): $m/z = 531$ $[M+H]^+$, 548 $[M+NH_4]^+$.

2.11. Methyl (2*R*,3*R*)-2-(*N*-*tert*-butoxycarbonyl)amino-3-hydroxy-15-methyl-hexadecanoate (2*R*,3*R*)-13 from (2*R*,3*R*)-11 or (2*R*,3*R*)-12

To a solution of crude (2*R*,*R*)-**11** (0.5 mmol) in methanol (4 mL) was added $NaHCO_3$ (160 mg, 1.9 mmol) and di-*tert*-butyl dicarbonate (120 mg, 0.55 mmol). The reaction vessel was immersed in an ultrasound cleaner filled with water and sonicated for 2 h. After evaporation of the solvent, purification of the residue by flash chromatography on silica gel (cyclohexane/ethyl acetate: 9/1 to 85/15) afforded (2*R*,3*R*)-**13** (189 mg, 91% from **9**) as a pale yellow solid. $[\alpha]_D^{25} = -14.4$ (*c* 1.0, $CHCl_3$). HPLC analysis: Chiralcel OD-H column; eluent, hexane/propan-2-ol: 99/1; flow rate: 1.0 mL/min; UV detection: 215 nm; t_R 21.17 min, (2*R*,3*R*)-**13**.

2.12. Methyl (2*S*,3*S*)-2-(*N*-*tert*-butoxycarbonyl)amino-3-hydroxy-15-methyl-hexadecanoate (2*S*,3*S*)-13 from (2*S*,3*S*)-11

Obtained as a pale yellow solid (192 mg, 92%) from crude (2*S*,3*S*)-**11** (0.5 mmol) according to the procedure described above for the preparation of (2*R*,3*R*)-**13**. $[\alpha]_D^{25} = +14.6$ (*c* 1.0, $CHCl_3$). HPLC analysis: Chiralcel OD-H column; eluent, hexane/propan-2-ol: 99/1; flow rate: 1.0 mL/min; UV detection: 215 nm; t_R 17.93 min, (2*S*,3*S*)-**13**.

2.13. Methyl (2*R*,3*R*)-2-(*N*-*tert*-butoxycarbonyl)amino-3-hydroxy-15-methyl-hexadecanoate (2*R*,3*R*)-13 from 14

To a solution of **14** (1.18 g, 2.22 mmol) in CH_2Cl_2 (20 mL) was added trifluoroacetic acid (14 mL) at room temperature. After stirring at room temperature for 3 h, the reaction mixture was concentrated and the residue was dried under vacuum to afford the deprotected hydrazine. The crude product was dissolved in absolute MeOH (12 mL) and a small spatula of activated W-2 Raney nickel (washed with water then MeOH) was added. The flask was flushed with hydrogen (1 atm), immersed in an ultrasound cleaner filled with water and sonicated for 14 h. The reaction mixture was then filtered on Celite under nitrogen and the Raney nickel washed with MeOH. After removal of the solvent, the crude product was purified by flash chromatography (cyclohexane/ethyl acetate/Et_3N: 95/5/2). The purified amine was dissolved in absolute MeOH (10 mL) and $NaHCO_3$ (500 mg, 6.0 mmol) and di-*tert*-butyl dicarbonate (480 mg, 2.32 mmol) were added. The mixture was sonicated in a cleaning bath until the end of CO_2 evolution (3.5 h), filtered, and concentrated. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate: 8/2) afforded (2*R*,3*R*)-**13** (738 mg, 80% from **14**) as a white solid, mp 38–40 °C. R_f 0.38 (cyclohexane/ethyl acetate 7/3). $[\alpha]_D^{25} = -18.9$ (*c* 0.99, $CHCl_3$). IR (KBr): 3560, 3467, 3416, 3370, 2919, 2852, 1752, 1687, 1685 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (d, 6H, $J = 6.6$ Hz), 1.14 (m, 2H), 1.24 (br s, 18H), 1.38–1.60 (m, 3H), 1.44 (s, 9H), 2.65 (br s, 1H, OH), 3.76 (s, 3H), 3.87 (m, 1H), 4.37 (m, 1H), 5.48 (br d, 1H, $J = 7.4$ Hz, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 25.8, 27.5, 28.0, 28.3, 29.5, 29.6, 29.7 (2C), 29.8, 30.0, 30.2, 33.4, 39.1, 52.5, 58.4, 73.2, 80.5, 156.0, 171.4. MS (DCI/NH_3): $m/z = 416$ $[M+H]^+$, 433 $[M+NH_4]^+$. Anal. Calcd for $C_{23}H_{45}NO_5$: C, 66.47; H, 10.91; N, 3.37. Found: C, 66.70; H, 11.24; N, 3.03. HPLC analysis: Chiralcel OD-H column; eluent, hexane/propan-2-ol: 99/1; flow rate: 1.0 mL/min; UV detection: 215 nm; t_R 21.17 min, (2*R*, 3*R*)-**13**.

2.14. Methyl 2-(*N*-*tert*-butoxycarbonyl)amino-15-methyl-3-oxo-hexadecanoate 15

To a solution of oxime **8** (5.6 g, 17.1 mmol) in acetic acid (64 mL) was added di-*tert*-butyl dicarbonate (45 mL, 196.0 mmol) and zinc (11.3 g, 172 mmol). After stirring at reflux for 3 h and at room temperature for 1.5 h, the solution was diluted with water, filtered on Celite, and rinsed with Et_2O. The layers were separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated. Purification of the residue by flash chromatography on silica gel (cyclohexane/ethyl acetate: 9/1) afforded **15** (5.8 g, 82%) as a pale yellow oil. R_f 0.78 (cyclohexane/ethyl acetate: 7/3). IR (film): 2924, 2852, 1757, 1711 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 6H, $J = 6.6$ Hz), 1.14 (m, 2H), 1.24 (br s, 16H), 1.43 (s, 9H), 1.51 (m, 1H), 1.58 (m, 2H),2.60 (dt, 1H, $J = 17.5$ and 7.2 Hz), 2.70 (dt, 1H, $J = 17.5$ and 7.2 Hz), 3.79 (s, 3H), 5.02 (d, 1H, $J = 7.1$ Hz), 5.71 (d, 1H, $J = 7.1$ Hz, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 23.5, 27.5, 28.2, 28.3, 29.0, 29.4, 29.5, 29.6, 29.7, 29.8, 30,0, 39.1, 40.6, 53.2, 63.6, 80.6, 155.0, 167.3, 201.5. MS (DCI/NH_3): $m/z = 358$ $[M-C_4H_8+H]^+$, 375 $[M-C_4H_8+NH_4]^+$, 414 $[M+H]^+$, 431 $[M+NH_4]^+$.

2.15. Methyl (2*S*,3*R*)-2-(*N*-*tert*-butoxycarbonyl)amino-3-hydroxy-15-methyl-hexadecanoate (2*S*,3*R*)-13

(*R*)-MeO-BIPHEP (7.0 mg, 0.012 mmol) and (COD)-Ru(2-methylallyl)$_2$ (3.2 mg, 0.01 mmol, commercially available from Acros) were placed in a round-bottomed tube, degassed by three vacuum/argon cycles at room temperature and dissolved in degassed acetone (1.5 mL). To this suspension was added at room temperature a 0.15 N methanolic hydrobromic acid solution (147 μL, 0.022 mmol) and the mixture was stirred at 25 °C for 30 min. After evaporation of the solvent under vacuum, a degassed solution of β-keto α-amino ester **15** (413.6 mg, 1.0 mmol) in CH_2Cl_2 (2 mL) was added via cannula to the ruthenium complex. The reaction vessel was placed in a stainless steel autoclave, which was purged with hydrogen and pressurized to 120 bar. The autoclave was heated to 50 °C by circulating thermostated water in the double wall and magnetic stirring was started as soon as the required temperature was reached. After stirring for 96 h, the autoclave was cooled to room temperature, hydrogen was vented, and the reaction mixture was concentrated in vacuo. Purification of the residue by flash chromatography (cyclohexane/ethyl acetate: 85/15) afforded β-keto-α-amino ester (2*S*,3*R*)-**13** (390.6 mg, 94%) as a pale yellow oil. R_f 0.34 (cyclohexane/ethyl acetate: 7/3). $[\alpha]_D^{25} = +2.7$ (*c* 1.0, $CHCl_3$). IR (film): 3431, 2925, 2853, 1752, 1716, 1696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 6H, $J = 6.6$ Hz), 1.15 (m, 2H), 1.25 (br s, 18H), 1.38–1.56 (m, 3H), 1.45 (s, 9H), 3.77 (s, 3H), 4.07 (m, 1H), 4.31 (br d, 1H, $J = 9.1$ Hz), 5.28 (br d, 1H, $J = 9.1$ Hz, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 25.6, 27.5, 28.0, 28.4, 29.5, 29.6, 29.7 (2C), 29.8, 30.0, 30.2, 33.8, 39.1, 52.6, 57.5, 72.2, 80.1, 156.1, 172.4. MS (DCI/NH_3): $m/z = 416$ $[M+H]^+$, 433 $[M+NH_4]^+$. Anal. Calcd for $C_{23}H_{45}NO_5$: C, 66.47; H, 10.91; N, 3.37. Found: C, 66.70; H, 11.24; N, 3.03. HPLC analysis: Chiralcel OD-H column; eluent, hexane/propan-2-ol: 99/1; flow rate: 1.0 mL/min; UV detection: 215 nm; t_R 19.21 min, (2*S*,3*R*)-**13**.

2.16. Methyl (2*R*,3*S*)-2-(*N*-*tert*-butoxycarbonyl)amino-3-hydroxy-15-methyl-hexadecanoate (2*R*,3*S*)-13

Obtained as a pale yellow oil (374.0 mg, 90%) from **15** (413.6 mg, 1.0 mmol) according to the procedure described above for the preparation of (2*S*,3*R*)-**13** using (*S*)-MeO-BIPHEP. R_f 0.34 (cyclohexane/ethyl acetate: 7/3). $[\alpha]_D^{25} = -2.5$ (*c* 1.0, $CHCl_3$). IR (film): 3431, 2925, 2853, 1752, 1716, 1696 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (d, 6H, $J = 6.6$ Hz), 1.15 (m, 2H), 1.25 (br s, 18H), 1.38–1.56 (m, 3H), 1.45 (s, 9H), 3.77 (s, 3H), 4.07 (m, 1H), 4.31 (br d, 1H, $J = 9.1$ Hz), 5.28 (br d, 1H, $J = 9.1$ Hz, NH). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.7, 25.6, 27.5, 28.0, 28.4, 29.5, 29.6, 29.7 (2C), 29.8, 30.0, 30.2, 33.8, 39.1, 52.6, 57.5, 72.2, 80.1, 156.1, 172.4. MS (DCI/NH_3): $m/z = 416$ $[M+H]^+$, 433 $[M+NH_4]^+$. Anal. Calcd for $C_{23}H_{45}NO_5$: C, 66.47; H, 10.91; N, 3.37. Found: C, 66.70; H, 11.24; N, 3.03. HPLC analysis: Chiralcel OD-H column; eluent, hexane/propan-2-ol: 99/1; flow rate: 1.0 mL/min; UV detection: 215 nm; t_R 20.15 min, (2*R*,3*S*)-**13**.

2.17. 3-*tert*-Butyl 4-methyl (4*R*,5*R*)-2,2-dimethyl-5-(12-methyl-tridecyl)-1,3-oxazolidine-3,4-dicarboxylate 16

To a solution of methyl (2*R*,3*R*)-2-(*N*-*tert*-butoxycarbonyl)amino-3-hydroxy-15-methyl-hexadecanoate (2*R*,3*R*)-**13** (642 mg, 1.55 mmol) in CH_2Cl_2 (5 mL) were added 2,2-dimethoxypropane (0.57 mL, 4.64 mmol) and $BF_3.Et_2O$ (10 μL, 0.077 mmol). After stirring at room temperature for 1 h, the mixture was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography on silica gel (cyclohexane/ethyl acetate: 8/2) afforded oxazolidine **16** (653 mg, 93%) as a pale yellow oil. R_f 0.64 (cyclohexane/ethyl acetate: 8/2). $[\alpha]_D^{25} = -14.0$ (*c* 0.83, $CHCl_3$). IR (film): 2921, 2852, 1750, 1710 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ 0.88 (d, 6H, $J = 6.6$ Hz), 1.18 (m, 2H), 1.28 (br s, 18H), 1.38–1.60 (m, 3H), 1.41 (s, 9H), 1.69 (s, 3H), 1.73 (s, 3H), 3.74 (s, 3H), 4.17 (dt, 1H, $J = 6.9$ and 4.9 Hz), 4.29 and 4.38 (2d, 1H, $J = 6.3$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$), two conformers: δ 22.5, 24.2, 25.0, 25.3, 26.0, 26.4, 27.3, 27.8, 28.2, 29.4, 29.8, 30.1, 38.9, 51.6, 62.7, 62.9, 75.5, 75.7, 80.0, 80.6, 93.8, 94.1, 151.0, 152.0, 170.5, 170.7. MS (DCI/NH_3): $m/z = 456$ $[M+H]^+$, 473 $[M+NH_4]^+$. Anal. Calcd for $C_{26}H_{49}NO_5$: C, 68.53; H, 10.84; N, 3.07. Found: C, 68.76; H, 11.02; N, 2.84.

2.18. *tert*-Butyl (4*R*,5*R*)-4-hydroxymethyl-2,2-dimethyl-5-(12-methyl-tridecyl)-1,3-oxazolidine-3-carboxylate 17

To a dispersion of $CaCl_2$ (1.0 g, 9.2 mmol) in THF (5.5 mL) was added a solution of ester **16** (600 mg,

1.32 mmol) in MeOH (9 mL). After cooling to −15 °C, $NaBH_4$ (598 mg, 15.8 mmol) was added and the mixture was stirred for 15 min at −15 °C and for 22 h at room temperature. Saturated aqueous Na_2SO_4 was added and the mixture was filtered on Celite, dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash chromatography on silica gel (cyclohexane/ethyl acetate: 8/2) afforded pure alcohol **17** (529 mg, 94%) as a pale yellow oil. R_f 0.29 (cyclohexane/ethyl acetate: 8/2). $[\alpha]_D^{25} = -6.5$ (*c* 0.79, $CHCl_3$). IR (film): 3459, 2927, 2852, 1680 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 50 °C) δ 0.88 (d, 6H, $J = 6.6$ Hz), 1.19 (m, 2H), 1.29 (br s, 18H), 1.38–1.60 (m, 3H), 1.50 (s, 9H), 1.57 (s, 3H), 1.58 (s, 3H), 3.65 (ddd, 1H, $J = 11.0$, 6.6, and 4.3 Hz), 3.82 (ddd, 1H, $J = 11.0$, 6.6, and 4.3 Hz), 3.99 (m, 1H), 4.05 (dt, 1H, $J = 7.4$ and 5.5 Hz). ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.5, 24.4, 26.3, 26.8, 27.3, 28.8, 29.5, 29.8, 27.8, 28.3, 38.9, 61.1, 63.2, 75.6, 81.0, 92.5, 155.0. MS (DCI, NH_3): $m/z = 428$ $[M+H]^+$. Anal. Calcd for $C_{25}H_{49}NO_4$: C, 70.21; H, 11.55; N, 3.28. Found: C, 70.30; H, 11.57; N, 3.18.

2.19. *tert*-Butyl (4*R*,5*R*)-4-acetylthiomethyl-2,2-dimethyl-5-(12-methyl-tridecyl)-1,3-oxazolidine-3-carboxylate 18

To a solution of PPh_3 (1.89 g, 7.21 mmol) in THF (22 mL) at 0 °C was added diisopropyl azodicarboxylate (1.48 mL, 7.04 mmol). After stirring at 0 °C for 4 h, a solution of alcohol **17** (1.49 g, 3.48 mmol) and thioacetic acid (0.55 mL, 7.66 mmol) in THF (15 mL) was added. The yellow mixture was then stirred 1 h at 0 °C and 15 h at room temperature. The reaction mixture was diluted with ethyl acetate (500 mL), washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$, filtered, and concentrated. Solid impurities were then removed by filtration after addition of pentane. Flash chromatography on silica gel (cyclohexane/ethyl acetate: 95/5) afforded pure thioester **18** (1.61 g, 95%) as a pale yellow oil. R_f 0.66 (cyclohexane/ethyl acetate: 8/2). $[\alpha]_D^{25} = +3.0$ (*c* 1.11, $CHCl_3$). IR (film): 2925, 2854, 1702, 1455, 1379 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), major conformer, δ 0.86 (d, 6H, $J = 6.6$ Hz), 1.15 (m, 2H), 1.26 (br s, 18H), 1.35-1.60 (m, 3H), 1.48 (s, 9H), 1.58 (s, 3H), 1.60 (s, 3H), 2.33 (s, 3H), 3.06 (dd, 1H, $J = 13.7$ and 4.1 Hz), 3.19 (dd, 1H, $J = 13.7$ and 6.6 Hz), 4.00 (m, 1H), 4.12 (m, 1H), minor conformer, δ 0.85 (d, 6H, $J = 6.6$ Hz), 1.15 (m, 2H), 1.26 (br s, 18H), 1.35–1.60 (m, 3H), 1.48 (s, 9H), 1.55 (s, 3H), 1.58 (s, 3H), 2.31 (s, 3H), 3.02 (dd, 1H, $J = 13.5$ and 5.5 Hz), 3.25 (dd, 1H, $J = 13.5$ and 6.3 Hz), 3.94 (m, 1H), 4.12 (m, 1H). ^{13}C NMR (50 MHz, $CDCl_3$), two conformers: δ 22.6, 23.3, 24.6, 26.4, 26.8, 26.9, 27.4, 27.6, 27.9, 28.3, 28.7, 28.9, 29.2, 29.4, 29.5, 29.6, 29.7, 29.9, 30.1, 30.5, 39.0, (58.5, 57.8), (80.2, 80.0), (92.9, 92.5), (152.3, 151.6), (195.0, 194.6). MS (DCI/NH_3): $m/z = 486$ $[M+H]^+$.

2.20. (2*R*,3*R*,3′*R*)-3-Hydroxy-2-(3′-hydroxy-15′-methyl-hexadecanoylamino)-15-methyl-hexadecan-1-sulfonic acid, sulfobacin A 1

To a solution of thioester **18** (90 mg, 0.19 mmol) in trifluoroacetic acid (0.5 mL) was carefully added at room temperature hydrogen peroxide (30% solution in water, 0.2 mL). After stirring at room temperature for 1 h, the reaction mixture was concentrated in vacuo. The crude yellow mixture was then crystallized by adding ethanol/water (1:2), filtered, and dried in vacuo to afford (2*R*,3*R*)-2-amino-3-hydroxy-15-methyl-hexadecan-1-sulfonic acid **19** as a white solid, which was used in the next step without further purification. To an ice cooled solution of (3*R*)-3-hydroxy-15-methyl-hexadecanoic acid **7** (51.6 mg, 0.18 mmol) and HONB (35.2 mg, 0.19 mmol) in THF/dioxane (1/1, 1.4 mL) was added DCC (39.4 mg, 0.19 mmol) and the mixture was stirred at 0 °C for 40 min, then at room temperature for 24 h. The resulting *N*,*N*′-dicyclohexylurea was filtered off, and the filtrate was concentrated in vacuo. The residue was dissolved in dioxane (1 mL), and a solution of the sodium salt of **19** [prepared by adding a solution of $NaHCO_3$ (16.6 mg, 0.20 mmol) in water (0.5 mL) to a solution of **19** (0.19 mmol) in dioxane (1 mL)] was added at room temperature. After stirring for 20 h, dioxane was evaporated in vacuo, the remaining aqueous solution was eluted through a column packed with Amberlite IR-120B (H^+ form) and eluted with MeOH/$CHCl_3$ (1/1) to afford a yellow solid after evaporation of the eluent. Purification of the solid by flash chromatography on silica gel ($CHCl_3$/MeOH: 10/0 to 6/4) yielded sulfobacin A **1** (23.6 mg, 20% from **18**) as a white solid, mp 230–231 °C, lit.[3] 220–222 °C, lit.[4] 233–235 °C. R_f 0.22 (low layer of $CHCl_3$/MeOH/H_2O: 65/25/10). $[\alpha]_D^{25} = -15.5$ (*c* 0.14, MeOH), lit.[1a] $[\alpha]_D^{24} = -35$ (*c* 0.14, MeOH), lit.[2] $[\alpha]_D^{20} = -7.9$ (*c* 0.18, MeOH), lit.[4a] $[\alpha]_D^{25} = -15$ (*c* 0.14, MeOH).[22] IR (KBr): 3356, 2950, 2850, 1642, 1554, 1467, 1198, 1054 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6) δ 0.83 (d, 12H, $J = 6.6$ Hz), 1.13 (m, 4H), 1.23 (m, 38H), 1.35 (m, 2H), 1.45 (m, 2H), 2.09 (dd, 1H, $J = 13.5$ and 5.5 Hz), 2.13 (dd, 1H, $J = 13.5$ and 6.7 Hz), 2.69 (dd, 1H, $J = 14.1$ and 4.3 Hz), 2.74 (dd, 1H, $J = 14.1$ and 6.7 Hz), 3.47 (m, 1H), 3.75 (m, 1H), 3.91 (m, 1H), 4.68 (d, 1H, $J = 4.4$ Hz), 4.79 (d, 1H, $J = 5.6$ Hz), 7.66 (d, 1H, $J = 8.8$ Hz). ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.7, 25.4, 25.7, 27.0, 27.6, 29.3, 29.4, 29.5, 29.6, 33.5, 36.8, 38.7, 45.0, 51.3, 52.0, 67.8, 72.1, 170.4.

Acknowledgements

We thank Dr. R. Schmid and Dr. M. Scalone (Hoffmann La Roche) for a generous gift of (*R*)- and (*S*)-MeO-BIPHEP: (*R*)-(+)- and (*S*)-(−)-6,6′-dimethoxy-2,2′-bis(diphenyl-phosphinoyl)-1,1′-biphenyl. O.L. is grateful to the Ministère de l'Education Nationale et de la Recherche for a grant (2001–2004).

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22. As mentioned earlier by Mori[4a] the specific rotation value of sulfobacin A seems to fluctuate depending on the concentration and the pH of the solution.