General Enantioselective Synthesis of Butyrolactone Natural Products *via* Ruthenium-SYNPHOS®-Catalyzed Hydrogenation Reactions

Delphine Blanc,[a] Jonathan Madec,[a] Florence Popowyck,[a] Tahar Ayad,[a] Phannarath Phansavath,[a,*] Virginie Ratovelomanana-Vidal,[a,*] and Jean-Pierre Genêt[a,*]

[a] Laboratoire de Synthèse Sélective Organique et Produits Naturels, Ecole Nationale Supérieure de Chimie de Paris, UMR 7573 CNRS, 11 rue Pierre et Marie Curie, 75231 Paris Cedex 05, France
Fax: (+33)-1-4407-1062; e-mail: jean-pierre-genet@enscp.fr, virginie-vidal@enscp.fr or phannarath-phansavath@enscp.fr

Abstract: Enantioselective syntheses of several paraconic acids have been achieved using catalyzed asymmetric hydrogenation of β-keto esters with SYNPHOS® as a ligand. This strategy allowed the short synthesis of biologically active (−)-methyleno-lactocin **1**, (−)-protolichesterinic acid **2**, (−)-phaseolinic acid **3** and (+)-roccellaric acid **4**.

Keywords: asymmetric catalysis; atropisomerism; hydrogenation; ruthenium; total synthesis

Introduction

Paraconic acids (3-carboxylic acid substituted γ-butyrolactones) are a class of trisubstituted γ-butyrolactones of biological significance exhibiting antibiotic and antitumor properties.[1] Their structural units frequently occur in natural products such as alkaloids, macrocyclic antibiotics and pheromones.[2] Consequently, they have attracted considerable interest over the years.[3] Characteristic features of this class of compounds are the C-4 carboxyl functionality as well as an alkyl chain at C-5, ranging in length from five to fifteen carbon atoms. The C-3 center, bearing a methylene or a methyl group, plays a vital role in the biological activity of the molecule (Scheme 1).

Due to their interesting biological properties, numerous syntheses of compounds **1–4** have been reported in both racemic and enantioselective versions, using the chiral pool,[4] chiral auxiliaries,[5] catalytic asymmetric methodologies,[6] or enzymatic routes.[7] However, many of these syntheses suffer from poor overall yields, large number of steps, and lack of generality. Our interest in the use of ruthenium-mediated asymmetric hydrogenation for the preparation of biologically relevant molecules[8] led us to study the development of a general strategy for the stereoselective synthesis of the paraconic acids **1–4**. Recently, we succeeded in designing and developing a new atropisomeric diphosphine named SYNPHOS®.[9] Our group has focused on expanding the versatile applications of
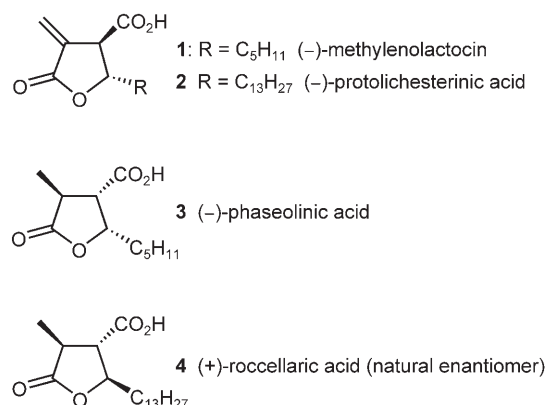

Scheme 1. Structures of paraconic acids **1–4**.

SYNPHOS® towards the synthesis of key intermediates for the preparation of target molecules of synthetic interest.[8] As part of our continuing interest in the homogeneous ruthenium-promoted hydrogenation reactions,[10] we report in this paper, a new application of SYNPHOS® ligand for a general route to paraconic acids using an Ru-SYNPHOS®-catalyzed asymmetric hydrogenation reaction as key step.

Our retrosynthetic analysis is based on ruthenium-catalyzed asymmetric hydrogenation of β-keto esters **6** or **13** to install the C-5 hydroxy-bearing stereocenter, followed by diastereoselective alkylation, lactonization, and finally methylation or methylenation at the C-3 center to give the desired paraconic acids **1–4**

(Scheme 2). Thus, *cis*-γ-butyrolactone **9** (R=C₅H₁₁) would serve as the common intermediate for the synthesis of (−)-methylenolactocin **1** and (−)-phaseolinic
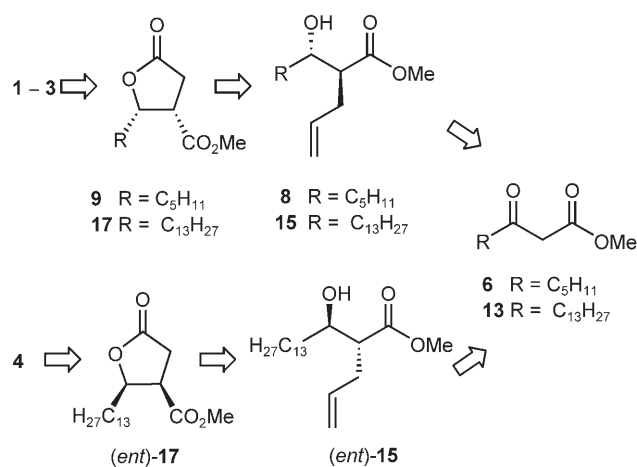

Scheme 2. Retrosynthetic analysis of paraconic acids **1-4**.

acid **3**, while (−)-protolichesterinic acid **2** would result from *cis*-γ-butyrolactone **17** (R=C₁₃H₂₇). Finally, (+)-roccellaric acid **4** would be obtained by methylation of *cis*-γ-butyrolactone (*ent*)-**17**, which would easily result from β-keto ester **13**. One relevant feature of this approach is that both enantiomers of lactones **9** and **17** could be synthesized with high enantio- and diastereoselectivities starting from the same β-keto esters **6** and **13**, respectively, using an asymmetric Ru-SYNPHOS®-mediated hydrogenation as the key step.

Results and Discussion

The synthesis of (−)-methylenolactocin **1** began with commercially available hexanoyl chloride **5** which was converted into the corresponding β-keto ester **6** using Wemple's procedure[11] (Scheme 3). Thus, treatment of **5** with monomethyl monopotassium malonate, magnesium chloride and triethylamine in acetonitrile, afforded **6** in 94% yield. The asymmetric hydrogenation of **6** was carried out under a low hydrogen pressure of 5 bar in methanol at S/C=200 by using the *in situ* generated {RuBr₂[(*S*)-SYNPHOS]®} complex[9e] prepared from a mixture of commercially available (COD)Ru(2-methylallyl)₂ and the diphosphine by addition of 2.2 equivs. of HBr according to our convenient procedure.[12] Under the above conditions, (*S*)-methyl 3-hydroxyoctanoate **7** was obtained in 96% yield and with excellent enantioselectivity (*ee* >99.5%).

Alkylation of **7** with allyl bromide using the Fráter–Seebach conditions[13] then afforded compound **8** in
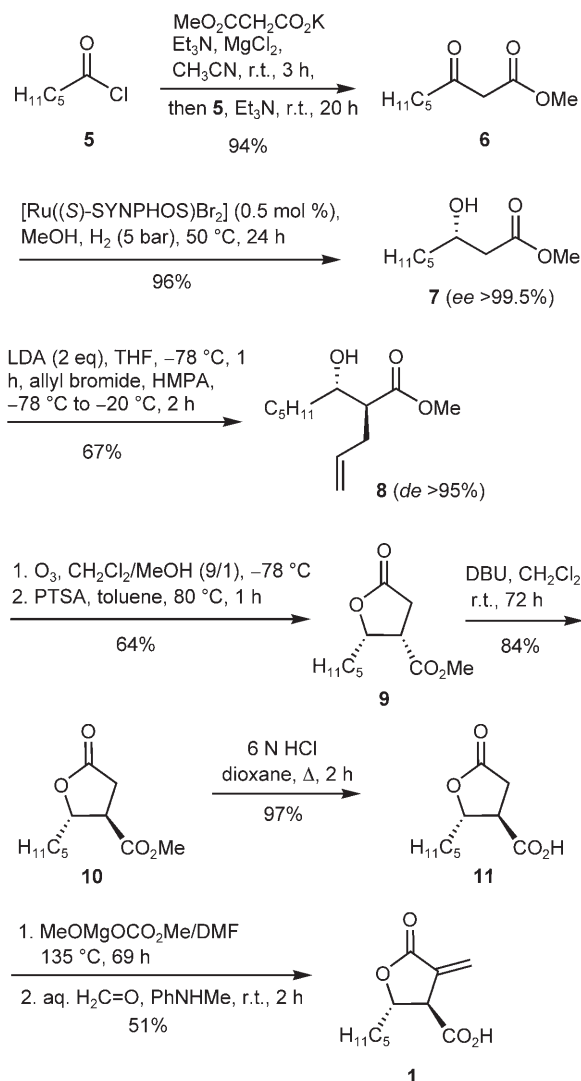
Scheme 3. Total synthesis of (−)-methylenolactocin **1**.

67% yield as a single diastereomer after flash chromatographic separation. Oxidation-lactonization of **8** was accomplished by ozonolysis in CH₂Cl₂/MeOH (9/1) followed by treatment with a catalytic amount of *p*-toluenesulfonic acid in toluene which gave the desired lactone **9** in 64% yield. The *trans*-lactone **10**, required for the synthesis of (−)-methylenolactocin **1** was prepared by treatment of **9** with DBU at room temperature to effect smooth equilibration into the C-4 epimeric lactone **10**. Subsequent hydrolysis of compound **10** yielded quantitatively the corresponding carboxylic acid **11**. For the introduction of the *exo*-methylene group at the C-3 center, we followed the procedure reported by Greene et al.[5h] Thus, compound **11** was treated with Stiles reagent[14] (magnesium methylcarbonate in DMF) at 135°C for 69 h, then with a solution of aqueous formaldehyde and *N*-methylaniline in the presence of sodium acetate to afford **1** in 51% yield. We have thus completed a

short synthesis of (−)-methylenolactocin **1** (seven steps from commercially available hexanoyl chloride) using ruthenium-SYNPHOS®-mediated hydrogenation as a key step to install the C-5 stereocenter with high enantioselectivity.

In an analogous way, (−)-protolichesterinic acid **2** and (+)-roccellaric acid **4** were synthesized starting from commercially available tetradecanoyl chloride **12** as depicted in Scheme 4. β-Keto ester **13** was first prepared in high yield from **12** by using Wemple's
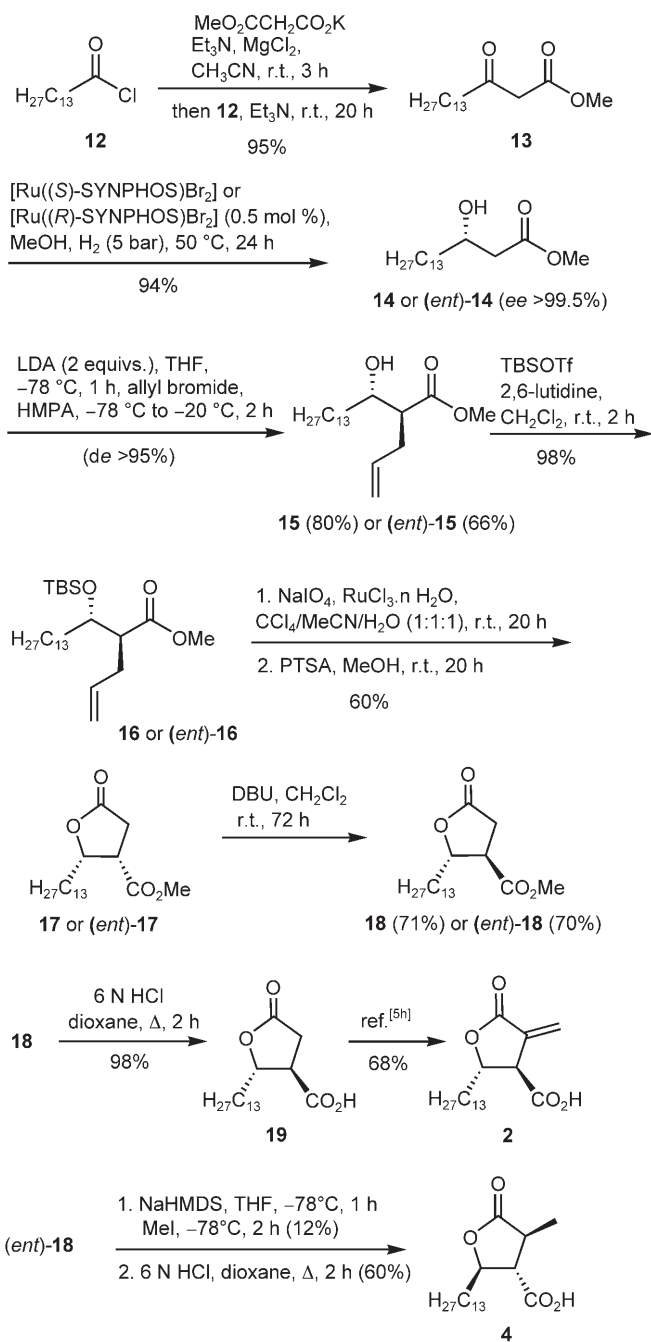
method. Then, asymmetric hydrogenation of **13** was performed in methanol at 50 °C under 5 bar of hydrogen and using either (S)- or (R)-SYNPHOS® as a ligand to afford respectively the corresponding β-hydroxy esters **14** and (ent)-**14** in 94% yield and with excellent enantioselectivity (ee >99.5%). Diastereoselective alkylation of **14** and (ent)-**14** with allyl bromide readily furnished respectively **15** and (ent)-**15** as single diastereomers after flash chromatographic separation. Ozonolysis of **15** was then performed using the same conditions as for the parent compound **8**. However, several attempts at ozonolysis resulted only in recovery of the starting material. Therefore, we decided to use the RuCl₃/NaIO₄ system for the oxidation of compound **15**. The oxidation-lactonization sequence was carried out after protection of **15** as its tert-butyldimethylsilyl ether **16**. Thus, exposure of **16** and (ent)-**16** to sodium periodate and catalytic ruthenium chloride in carbon tetrachloride/acetonitrile/water (1/1/1), followed by treatment with para-toluenesulfonic acid in methanol, afforded respectively γ-butyrolactones **17** and (ent)-**17**, which underwent smooth equilibration into trans-lactones **18** and (ent)-**18** in the presence of DBU.

Subsequent hydrolysis of compound **18** furnished the corresponding carboxylic acid **19** in 98% yield. This compound has been previously converted into (−)-protolichesterinic acid **2** by Greene et al.[5h] in 68% yield. We have thus completed a formal total synthesis of **2** in good overall yield (32%) and with very high enantio- and diastereoselectivities. A total synthesis of (+)-roccellaric acid **4** was achieved as well starting from (ent)-**18**. Diastereoselective methylation of lactone (ent)-**18** proceeded in very low yield.[17] Hydrolysis of the methylated compound finally afforded the natural product in 60% yield.

(−)-Phaseolinic acid **3** was prepared from the previously synthesized syn-lactone **9** (Scheme 5) following the two-step sequence already used for the preparation of compound **4**. Thus, the methyl group at the C-3 stereocenter was set in good yield and in a highly

Scheme 4. Total synthesis of (−)-protolichesterinic acid **2** and (+)-roccellaric acid **4**.
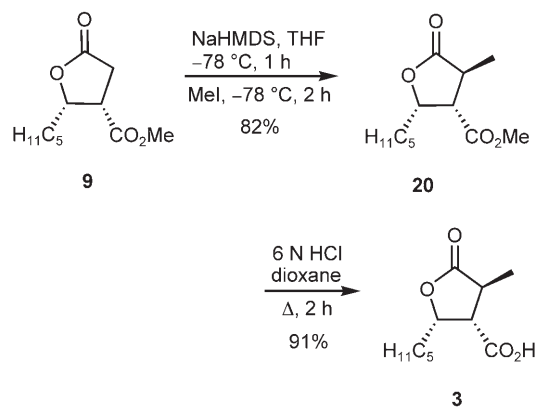
Scheme 5. Synthesis of (−)-phaseolinic acid **3**.

diastereoselective manner by treatment with NaHMDS/methyl iodide, and subsequent hydrolysis finally delivered (−)-phaseolinic acid **3** in 91% yield.

Conclusions

In summary, we have developed a concise and efficient enantioselective synthesis towards a variety of paraconic acids using catalytic asymmetric hydrogenation of achiral β-keto esters as the key step to set the hydroxy function at the C-5 stereocenter. We have shown that the SYNPHOS® ligand can be efficiently used in these transformations, providing the development of a general route to trisubstituted γ-butyrolactones. This flexible method allowed the synthesis of four members of the paraconic acids class, which were obtained in seven to nine steps starting from inexpensive acid chlorides (for comparison, the other reported syntheses generally involve up to fourteen steps, and only four steps for the shortest one).

Experimental Section

General Remarks

All solvents were reagent grade and distilled under positive pressure of argon prior to use. Amines and CH_2Cl_2 were distilled from calcium hydride. THF was distilled from sodium-benzophenone. Unless specially mentioned, 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 MHz and 50 MHz, respectively, on an AC200 Brüker spectrometer, or at 400 MHz and 100 MHz, respectively, on an ARX400 Brüker spectrometer. Infrared spectra (IR) were recorded on either a Perkin–Elmer 783G spectrometer or an IRFT Nicolet 205 spectrometer. Mass spectra (MS) were measured on a Hewlett–Packard 5989 A (70 eV) mass spectrometer. 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 either by UV light at 254 nm or by a potassium permanganate solution. Melting points (mp) were determined on a Kofler melting point apparatus and are uncorrected. Optical rotation values were measured with a Perkin–Elmer 241 polarimeter. High performance liquid chromatography analyses (HPLC) were performed on a Waters instrument (Waters 486 detector, 717 autosampler). Elemental analysis was performed by the Service Régional de Microanalyse de l'Université Pierre et Marie Curie.

General Procedure for the Asymmetric Hydrogenation of β-Keto Esters

(R)- or *(S)*-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 mL). To this suspension was added at room temperature a 0.15 N methanolic HBr 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 solution of β-keto ester (2 mmol) in MeOH (2 mL) was added to the ruthenium catalyst. The resulting mixture was placed under the desired hydrogen pressure and temperature for 24 h. After removal of the solvent, the residue was purified by flash chromatography on silica gel to afford the β-hydroxy ester.

Methyl 3-Oxooctanoate (6)

To a suspension of potassium methyl malonate (14.3 g, 92.0 mmol) in CH_3CN (125 mL) at 5°C was added Et_3N (12.4 mL, 88.7 mmol) followed by anhydrous $MgCl_2$ (10.6 g, 111.4 mmol). The mixture was stirred at room temperature for 3 h, then cooled to 0°C and hexanoyl chloride (5.7 g, 42.0 mmol) was added dropwise followed by the addition of more Et_3N (1.38 mL, 9.8 mmol). The mixture was allowed to stir for 20 h at room temperature and concentrated. Et_2O (100 mL) was added to the resulting solid followed by 6 N HCl until complete dissolution of the precipitate. The aqueous layer was separated and extracted with Et_2O. The combined organic layers were washed with saturated Na_2CO_3 followed by brine, dried ($MgSO_4$) and concentrated under vacuum. The residue was purified by Kugelrohr distillation (bp 88°C/0.4 torr) to give **6** as a colorless oil; yield: 6.8 g (94%); IR (neat): $\nu = 1750$, 1720 cm^{-1}; ^1H NMR (200 MHz, CDCl$_3$): $\delta = 11.94$ (s, 1H, enol form), 4.90 (s, 1H, enol form), 3.64 (s, 3H), 3.37 (s, 2H), 2.45 (t, 2H, $J = 7.3$ Hz), 1.50 (m, 2H), 1.21 (m, 4H), 0.80 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR (50 MHz, CDCl$_3$): $\delta = 202.6$, 167.5, 51.9, 48.7, 42.7, 30.9, 22.9, 22.2, 13.6; MS (EI): $m/z = 172$ [M$^+$].

(S)-Methyl 3-Hydroxyoctanoate (7)

Methyl 3-oxooctanoate **6** (10.0 g, 58.1 mmol) was hydrogenated according to the general procedure for hydrogenation, using 0.5 mol% of the catalyst [Ru((S)-SYNPHOS)Br$_2$] in MeOH (5 mL) at 50°C under 5 bar of hydrogen for 24 h. The reaction mixture was concentrated and the residue was purified by Kugelrohr distillation (bp 140°C/2 torr) to afford **7** as a colorless oil; yield: 9.7 g (96%); $[\alpha]_D^{20}$: +22.4 (c 2.0, CHCl$_3$), lit.[15] $[\alpha]_D^{24}$: +24 (c 1.0, CHCl$_3$); IR (neat): $\nu = 3400$ (broad), 1735 cm^{-1}; ^1H NMR (200 MHz, CDCl$_3$): $\delta = 4.03$ (m, 1H), 4.74 (s, 3H), 2.92 (d, 1H, $J = 4.0$ Hz), 2.55 (dd, 1H, $J = 16.4$ and 3.6 Hz), 2.42 (dd, 1H, $J = 16.4$ and 8.5 Hz), 1.60–1.25 (m, 8H), 0.91 (t, 3H, $J = 6.4$ Hz); ^{13}C NMR (50 MHz, CDCl$_3$): $\delta = 173.3$, 67.8, 51.5, 41.1, 36.4, 31.5, 25.0, 22.4, 13.8; MS (EI): $m/z = 175$ [M$^+ + 1$]; anal. calcd. for C$_9$H$_{18}$O$_3$ (174.24): C 62.04, H 10.41; found: C 61.96, H 10.44. HPLC analysis (of the corresponding acetate): column, Chiralcel AS-H; eluent, hexane/propan-2-ol, 98/2; flow rate: 1.0 mL min^{-1}; detection: 215 nm, t_R: 6.78 min, (S)-**7**, t_R: 7.32 min, (R)-**7**.

(2S,3S)-Methyl 2-Allyl 3-hydroxyoctanoate (8)

To a solution of LDA (70.4 mmol) in THF was added dropwise at −78°C a solution of **7** (5.0 g, 28.7 mmol) in THF (68 mL). The mixture was stirred at −78°C for 1 h and allyl

bromide (6.3 mL, 71.8 mmol) was added followed by HMPA (9.3 mL, 51.7 mmol). After being stirred for 1 h at −78 °C, the reaction mixture was slowly warmed to −20 °C, stirred at this temperature for 1 h and saturated NaHCO$_3$ was added at 0 °C followed by Et$_2$O. A 10% HCl solution was slowly added until pH 2 and the aqueous layer was extracted with Et$_2$O. The combined organic layers were washed with water and brine, dried (MgSO$_4$) and concentrated under vacuum. Purification of the residue by flash chromatography (1 to 10% AcOEt in cyclohexane) afforded **8** as a colorless oil; yield: 4.1 g (67%); $[\alpha]_D^{20}$: −4.2 (c 1.05, CHCl$_3$); IR (neat): $\nu = 3400$ (broad), 1740, 1660 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 5.76$ (ddt, 1H, $J = 17.0$, 10.1 and 7.0 Hz), 5.05 (m, 2H), 3.73 (s, 3H), 3.75–3.60 (m, 1H), 2.62–2.38 (m, 4H), 1.50–1.20 (m, 8H), 0.91 (t, 3H, $J = 6.4$ Hz); ^{13}C NMR (50 MHz, CDCl$_3$): $\delta = 175.1$, 134.7, 117.0, 71.6, 51.4, 50.4, 35.3, 33.6, 31.5, 25.2, 22.4, 13.8; MS (EI): $m/z = 215$ [M$^+$+1].

(3S,4S)-3-Methoxycarbonyl-4-pentyl-γ-butyrolactone (9)

At −78 °C, a stream of ozone was bubbled through a solution of **8** (500 mg, 2.33 mmol) in CH$_2$Cl$_2$/MeOH (9/1 mL) until a persistent blue color was perceived. The excess of ozone was then chased away by bubbling argon through the solution to give a colorless mixture which was concentrated. The crude residue was dissolved in toluene and a catalytic amount of PTSA was added. The reaction mixture was stirred at 80 °C for 1 h and concentrated. Purification of the residue by flash chromatography (10% to 40% AcOEt in cyclohexane, water deactivated silica gel) afforded **9** as a yellow solid; yield: 319 mg (64%); $[\alpha]_D^{20}$: −81 (c 0.97, CHCl$_3$), lit.[5h] $[\alpha]_D^{21}$: −78 (c 1.0, CHCl$_3$); IR (CH$_2$Cl$_2$): $\nu = 1790$, 1745 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 4.63$ (m, 1H), 3.76 (s, 3H), 3.45 (ddd, 1H, $J = 8.6$, 7.3 and 5.6 Hz), 2.91 (dd, 1H, $J = 17.6$ and 5.6 Hz), 2.67 (dd, 1H, $J = 17.6$ and 8.6 Hz), 1.70–1.20 (m, 8H), 0.91 (m, 3H); ^{13}C NMR (50 MHz, CDCl$_3$): $\delta = 174.8$, 170.7, 80.4, 52.2, 44.2, 31.7 (2C), 31.3, 25.4, 22.4, 13.9; MS (EI): $m/z = 215$ [M$^+$+1]; anal. calcd. for C$_{11}$H$_{18}$O$_4$ (214.26): C 61.66, H 8.47; found: C 61.76, H 8.37.

(3R,4S)-3-Methoxycarbonyl-4-pentyl-γ-butyrolactone (10)

To a solution of **9** (154 mg, 0.72 mmol) in CH$_2$Cl$_2$ (10 mL) was added DBU (258 µL, 1.72 mmol) and the resulting mixture was stirred at room temperature for 72 h, diluted with AcOEt and washed with saturated NH$_4$Cl. The organic layer was separated, washed with brine, dried (MgSO$_4$) and concentrated under vacuum. The crude product was purified by flash chromatography (10% to 20% AcOEt in cyclohexane) to afford **10** as a white solid; yield: 129 mg (84%); $[\alpha]_D^{20}$: −55 (c 1.1, CHCl$_3$), lit.[5i] $[\alpha]_D^{20}$: −56 (c 1.0, CHCl$_3$); IR (CH$_2$Cl$_2$): $\nu = 1790$, 1740 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 4.58$ (q, 1H, $J = 7.1$ Hz), 3.77 (s, 3H), 3.03 (m, 1H), 2.92 (dd, 1H, $J = 17.7$ and 8.8 Hz), 2.77 (dd, 1H, $J = 17.7$ and 9.5 Hz), 1.81–1.70 (m, 2H), 1.50–1.28 (m, 6H), 0.90 (t, 3H, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 174.5$, 171.5, 82.0, 52.8, 45.8, 35.4, 32.3, 31.4, 24.9, 22.5, 14.0; MS (CI, NH$_3$): $m/z = 232$ [M$^+$+NH$_4$].

(3R,4S)-3-Carboxy-4-pentyl-γ-butyrolactone (11)

To a solution of **10** (126 mg, 0.59 mmol) in dioxane (6.3 mL) was added 6 N HCl (3.6 mL) at room temperature. The mixture was refluxed for 2 h and concentrated under vacuum. An acid/base treatment then furnished **11** as a white solid; yield: 114 mg (97%); $[\alpha]_D^{20}$: −52 (c 0.5, CHCl$_3$), lit.[5i] $[\alpha]_D^{20}$: −54 (c 0.5, CHCl$_3$); IR (CH$_2$Cl$_2$): $\nu = 1760$, 1725 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.96$ (br s, 1H), 4.62 (q, 1H, $J = 7.0$ Hz), 3.05 (m, 1H), 2.93 (dd, 1H, $J = 17.9$ and 8.4 Hz), 2.82 (dd, 1H, $J = 17.9$ and 9.6 Hz), 1.90–1.20 (m, 8H), 0.89 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 176.6$, 174.8, 82.2, 45.8, 35.7, 32.3, 31.7, 25.2, 22.8, 14.3; MS (CI, NH$_3$): $m/z = 218$ [M$^+$+NH$_4$].

(−)-Methylenolactocin (1)

A 2 M solution of methoxymagnesium methyl carbonate in DMF (3.7 mL, 7.16 mmol) was added to **11** (42 mg, 0.21 mmol) and the mixture was stirred at 135 °C for 69 h, hydrolyzed with 10 N HCl and extracted with CH$_2$Cl$_2$. The combined organic layers were dried (MgSO$_4$) and concentrated under vacuum. To the crude product was added an aqueous solution (330 µL) of formaldehyde and N-methylaniline [prepared by mixing acetic acid (5.0 mL), a solution of 30% formaldehyde in H$_2$O (4.6 mL), N-methylaniline (1.3 mL) and sodium acetate (150 mg)] and the mixture was stirred at room temperature for 2 h, diluted with CH$_2$Cl$_2$, washed with brine, dried (MgSO$_4$) and concentrated. Purification of the residue by flash chromatography (CHCl$_3$/AcOEt/AcOH: 90/8/2) furnished **1** as a white solid; yield: 23 mg (51%); $[\alpha]_D^{20}$: −10 (c 0.5, MeOH), lit.[5i] $[\alpha]_D^{20}$: −6.8 (c 0.5, MeOH); IR (CH$_2$Cl$_2$): $\nu = 1760$, 1710 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 8.95$ (br s, 1H), 6.46 (d, 1H, $J = 2.9$ Hz), 6.02 (d, 1H, $J = 2.6$ Hz), 4.81 (m, 1H), 3.62 (td, 1H, $J = 5.7$ and 2.8 Hz), 1.80–1.65 (m, 2H), 1.60–1.22 (m, 6H), 0.90 (t, 3H, $J = 6.6$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 172.4$, 168.2, 132.6, 125.8, 78.9, 49.4, 35.8, 31.4, 24.5, 22.5, 14.0; MS (EI): $m/z = 213$ [M$^+$+1].

Methyl 3-Oxohexadecanoate (13)

Starting from tetradecanoyl chloride (4.8 g, 19.6 mmol) and following the procedure described for the preparation of compound **6**, ester **13** was obtained after flash chromatography (10% AcOEt in cyclohexane) as a white solid; yield: 5.3 g (94%); mp 39–40 °C; IR (KBr): $\nu = 1750$, 1725 cm^{-1}; ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 3.77$ (s, 3H), 3.47 (s, 2H), 2.55 (t, 2H, $J = 7.2$ Hz), 1.59 (m, 2H), 1.45 (m, 20H), 0.91 (t, 3H, $J = 6.7$ Hz); ^{13}C NMR (50 MHz, CDCl$_3$): $\delta = 202.1$, 173.6, 52.2, 48.9, 42.9, 31.8, 29.2 (8C), 23.4, 22.6, 14.0; MS (EI): $m/z = 285$ [M$^+$+1]; anal. calcd. for C$_{17}$H$_{32}$O$_3$ (284.44): C 71.79, H 11.34; found: C 71.96, H 11.25.

(S)-Methyl 3-Hydroxyhexadecanoate (14) and (R)-Methyl 3-Hydroxyhexadecanoate [(ent)-14]

Methyl 3-oxohexadecanoate **13** (4.0 g, 14.0 mmol) was hydrogenated according to the general procedure for hydrogenation, using 0.5 mol% of [Ru((S)-SYNPHOS)Br$_2$] in MeOH (15 mL) at 50 °C under 5 bar of hydrogen for 24 h. The reaction mixture was concentrated and the residue was purified by flash chromatography (15 to 25% AcOEt in cy-

clohexane) to afford **14** as a white solid; yield: 3.8 g (94 %); mp 52 °C; $[\alpha]_D^{20}$: +6.1 (c 1.1, CHCl₃), lit.[16] $[\alpha]_D^{20}$: +13.5 (c 2.09, CHCl₃).

Compound (*ent*)-**14**: white solid, mp 51–53 °C; $[\alpha]_D^{20}$: −6.0 (c 1.0, CHCl₃), lit.[8e] $[\alpha]_D^{25}$: −16.6 (c 1.0, CHCl₃); IR (KBr): ν = 3300 (broad), 1750 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ = 4.04 (m, 1H), 3.74 (s, 3H), 2.89 (d, 1H, J = 4.0 Hz), 2.55 (dd, 1H, J = 16.4 and 3.6 Hz), 2.42 (dd, 1H, J = 16.4 and 8.6 Hz), 1.45 (m, 2H), 1.28 (m, 22H), 0.91 (t, 3H, J = 6.6 Hz); ¹³C NMR (50 MHz, CDCl₃): δ = 173.6, 68.1, 51.8, 41.2, 36.6, 32.0, 29.7 (8C), 25.6, 22.8, 14.2; MS (CI, NH₃): m/z = 304 [M⁺+NH₄], 287 [M⁺+1]; anal. calcd. for C₁₇H₃₄O₃ (286.45): C 71.28, H 11.96; found: C 71.23, H 11.84. HPLC analysis (of the corresponding benzoate): column, Chiralcel OD-H; eluent, hexane/propan-2-ol 99/1; flow rate: 1.0 mL min⁻¹; detection: 215 nm; t_R: 7.30 min, **14**, t_R: 8.05 min, (*ent*)-**14**.

(2S,3S)-Methyl 2-Allyl 3-hydroxyhexadecanoate (15) and (2R,3R)-Methyl 2-Allyl 3-hydroxyhexadecanoate [(ent)-15]

Starting from (*S*)-methyl 3-hydroxy-hexadecanoate **14** (5.7 g, 20 mmol) and following the procedure described for the preparation of compound **8**, ester **15** was obtained after flash chromatography (5 % AcOEt in cyclohexane) as a white solid; yield: 5.2 g (80 %); mp 36–38 °C; $[\alpha]_D^{20}$: −2 (c 1.2, CHCl₃).

Compound (*ent*)-**15**: white solid; mp 38–40 °C; $[\alpha]_D^{20}$: +4 (c 1.1, CHCl₃). IR (KBr): ν = 3400 (broad), 1725, 1650 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ = 5.78 (ddt, 1H, J = 17.0, 10.1 and 6.9 Hz), 5.10 (m, 2H), 3.73 (s, 3H), 3.70 (m, 1H), 2.65–2.40 (m, 4H), 1.48 (m, 2H), 1.28 (m, 22H), 0.91 (t, 3H, J = 6.3 Hz); ¹³C NMR (50 MHz, CDCl₃): δ = 175.2, 134.8, 116.9, 71.8, 51.4, 50.5, 35.3, 33.6, 31.6, 29.6 (5C), 29.5, 29.4, 29.1, 25.2, 22.4, 13.9; MS (EI): m/z = 327 [M⁺+1]; anal. calcd. for C₂₀H₃₈O₃ (326.52): C 73.57, H 11.73; found: C 73.76, H 11.65.

(2S,3S)-Methyl 2-Allyl-3-tert-butyldimethylsiloxyhexadecanoate (16)

To a solution of **15** (326 mg, 1.0 mmol) in CH₂Cl₂ (1 mL) were added *tert*-butyldimethylsilyl trifluoromethanesulfonate (345 μL, 1.5 mmol) and 2,6-lutidine (235 μL, 2.0 mmol). The mixture was stirred at room temperature for 2 h, quenched with brine and extracted with AcOEt. The combined organic layers were washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude product was purified by flash chromatography (5 % AcOEt in cyclohexane) to afford **16** as a pale yellow oil; yield: 431 mg (98 %); $[\alpha]_D^{20}$: +11.7 (c 1.07, CHCl₃); IR (thin film): ν = 1742, 1650, 1254, 835 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ = 5.75 (ddt, 1H, J = 16.8, 10.0 and 7.0 Hz), 5.78 (m, 2H), 3.90 (m, 1H), 3.63 (s, 3H), 2.70–2.20 (m, 3H), 1.48 (m, 24H), 0.89–0.83 (m, 12H), 0.02 (s, 6H); ¹³C NMR (50 MHz, CDCl₃): δ = 173.9, 135.8, 116.1, 72.6, 51.2, 51.1, 33.5, 31.8, 31.5, 29.6 (9C), 29.5, 29.4, 29.1, 25.6, 24.0, 22.5, 17.8, 13.9; MS (CI, NH₃): m/z = 441 [M⁺+1]; anal. calcd. for C₂₆H₅₂O₃Si (440.79): C 70.8, H 11.9; found: C 70.66, H 12.05.

(3S,4S)-3-Methoxycarbonyl-4-tridecyl-γ-butyrolactone (17) and (3R,4R)-3-Methoxycarbonyl-4-tridecyl-γ-butyrolactone [(ent)-17]

To a suspension of **16** (1.76 g, 4.0 mmol) and sodium periodate (3.4 g, 16 mmol) in a 1/1/1 mixture of CCl₄/MeCN/H₂O (60 mL) was added ruthenium trichloride hydrate (70 mg, 0.26 mmol) and the mixture was stirred vigorously for 20 h at room temperature. After extraction with Et₂O, the combined organic layers were washed with brine, dried (MgSO₄) and concentrated under vacuum. The crude product was dissolved in MeOH (100 mL) and *p*-toluenesulfonic acid (190 mg, 1 mmol) was added. The mixture was stirred at room temperature for 20 h and concentrated. The residue was purified by flash chromatography (10 to 40 % AcOEt in cyclohexane) to afford **17** as a white solid; yield: 782 mg (60 %); mp 68–70 °C; $[\alpha]_D^{20}$: −58 (c 1.0, CHCl₃).

Compound (*ent*)-**17**: white solid; mp 70–72 °C; $[\alpha]_D^{20}$: +59 (c 1.2, CHCl₃); IR (KBr): ν = 1775, 1730 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ = 4.64 (m, 1H), 3.77 (s, 3H), 3.46 (ddt, 1H, J = 8.6, 7.3 and 5.6 Hz), 2.93 (dd, 1H, J = 17.6 and 5.6 Hz), 2.68 (dd, 1H, J = 17.6 and 8.6 Hz), 1.57 (m, 2H), 1.27 (m, 22H), 0.90 (t, 3H, J = 6.6 Hz); ¹³C NMR (50 MHz, CDCl₃): δ = 174.8, 170.7, 80.3, 52.1, 44.2, 31.8, 31.7, 31.3, 29.5 (6C), 29.2, 29.1, 25.7, 22.6, 14.0; MS (CI, NH₃): m/z = 344 [M⁺+NH₄], 327 [M⁺+1]; anal. calcd. for C₁₉H₃₄O₄ (326.47): C 69.90, H 10.50; found: C 69.99, H 10.51.

(2S,3R)-Methyl 5-Oxo-2-tridecyltetrahydrofuran-3-carboxylate (18) and (2R,3S)-Methyl 5-Oxo-2-tridecyltetrahydrofuran-3-carboxylate [(ent)-18]

Starting from (3S,4S)-3-methoxycarbonyl-4-tridecyl-γ-butyrolactone **17** (751 mg, 2.3 mmol) and following the procedure described for the preparation of compound **10**, ester **18** was obtained after flash chromatography (10 to 30 % AcOEt in cyclohexane) as a white solid; yield: 533 mg (71 %); mp 44 °C; $[\alpha]_D^{20}$: −78 (c 1.0, CHCl₃).

Compound (*ent*)-**18**: white solid; mp 45 °C; $[\alpha]_D^{20}$: +80 (c 1.08, CHCl₃); IR (KBr): ν = 1775, 1735 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ = 4.58 (m, 1H), 3.77 (s, 3H), 3.05 (m, 1H), 2.92 (dd, 1H, J = 18.0 and 8.6 Hz), 2.78 (dd, 1H, J = 18.0 and 9.5 Hz), 1.74 (m, 2H), 1.50–1.28 (m, 22H), 0.90 (t, 3H, J = 6.8 Hz); ¹³C NMR (50 MHz, CDCl₃): δ = 174.2, 171.4, 81.8, 52.5, 45.5, 35.2, 32.0, 31.7, 29.5 (6C), 29.2, 29.1, 25.0, 22.5, 14.0; MS (CI, NH₃): m/z = 344 [M⁺+NH₄]; 327 [M⁺+1]; anal. calcd. for C₁₉H₃₄O₄ (326.47): C 69.90, H 10.50; found: C 70.0, H 10.5.

(2S,3R)-5-Oxo-2-tridecyltetrahydrofuran-3-carboxylic Acid (19)

Starting from (2S,3R)-methyl 5-oxo 2-tridecyltetrahydrfuran-3-carboxylate **18** (440 mg, 1.3 mmol) and following the procedure described for the preparation of compound **11**, acid **19** was obtained as a white solid; yield: 413 mg (98 %); mp 109–110 °C; $[\alpha]_D^{20}$: −40 (c 0.5, CHCl₃); IR (KBr): ν = 1775, 1730 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ = 4.64 (q, 1H, J = 7.0 Hz), 3.15 (m, 1H), 2.92 (dd, 1H, J = 18.0 and 8.5 Hz), 2.78 (dd, 1H, J = 18.0 and 9.5 Hz), 1.60 (m, 2H), 1.50–1.20 (m, 22H), 0.90 (t, 3H, J = 6.8 Hz); ¹³C NMR (50 MHz, CDCl₃): δ = 176.5, 174.5, 81.8, 45.5, 35.5, 31.8, 31.3, 29.5 (6C), 29.2, 29.1, 25.7, 22.5, 14.0; MS (CI, NH₃):

$m/z = 330$ [$M^+ + NH_4$], 313 [$M^+ + 1$]; anal. calcd. for $C_{18}H_{32}O_4$ (312.45): C 69.15, H 10.32; found: C 69.08, H 10.23.

(+)-Roccellaric Acid (4)

To a 1 M solution of NaHMDS in THF (6.4 mL, 6.4 mmol) was added at $-78\,^{\circ}$C a solution of *ent*-**18** (979 mg, 3 mmol) in THF (6 mL). The mixture was stirred at $-78\,^{\circ}$C for 1 h then methyl iodide (1.7 µL, 27 mmol) was added dropwise. After being stirred for 2 h, the reaction mixture was warmed to $-20\,^{\circ}$C, hydrolyzed with 1 N HCl, and extracted with Et$_2$O. The combined organic layers were washed with brine, dried (MgSO$_4$) and concentrated under vacuum. The crude product was purified by flash chromatography (5 % to 20 % AcOEt in cyclohexane) to afford (2*S*,3*S*,4*S*)-methyl 4-methyl 5-oxo-2-tridecyltetrahydrofuran-3-carboxylate as a white solid; yield: 115 mg (12 %).

A solution of (2*S*,3*S*,4*S*)-methyl 4-methyl-5-oxo-2-tridecyl-tetrahydrofuran-3-carboxylate (50 mg, 0.147 mmol) and 6 N HCl (1.5 mL) in dioxane (3 mL) was then refluxed for 4 h, cooled and concentrated. Purification of the residue by flash chromatography (70 % AcOEt in cyclohexane) afforded **4** as a white solid; yield: 29 mg (60 %); mp 112 °C; $[\alpha]_D^{20}$: +21.4 (*c* 0.5, CHCl$_3$), lit.[6f] $[\alpha]_D^{25}$: +26.2 (*c* 1.6, CHCl$_3$); ^{1}H NMR (200 MHz, CDCl$_3$): $\delta = 4.48$ (m, 1H), 2.97 (m, 1H), 2.69 (m, 1H), 1.89–1.65 (m, 2H), 1.36 (d, 3H, $J = 6.9$ Hz), 1.40–1.18 (m, 22H), 0.87 (t, 3H, $J = 6.5$ Hz); ^{13}C NMR (50 MHz, CDCl$_3$): $\delta = 176.5$, 175.6, 79.3, 53.8, 39.7, 34.8, 31.8, 29.5 (5C), 29.4, 29.2, 29.1, 25.2, 22.6, 14.4, 14.0.

(2*S*,3*S*,4*S*)-3-Methoxycarbonyl-2-methyl-4-pentyl-γ-butyrolactone (20)

Starting from **9** (30 mg, 0.14 mmol) and following the procedure described above for the preparation of (2*S*,3*S*,4*S*)-methyl 4-methyl 5-oxo 2-tridecyltetrahydrofuran-3-carboxylate, lactone **20** was obtained after flash chromatography (5 % to 30 % AcOEt in cyclohexane) as a white solid; yield: 26 mg (82 %); $[\alpha]_D^{20}$: −89 (*c* 0.75, CH$_3$CN), lit.[1c] $[\alpha]_D^{20}$: −82 (*c* 0.3, CH$_3$CN); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 4.65$ (m, 1H), 3.77 (s, 3H), 3.25–3.00 (m, 2H), 1.30 (d, 3H, $J = 6.8$ Hz), 1.60–1.26 (m, 8H), 0.85 (t, 3H, $J = 6.3$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 177.7$, 170.2, 77.6, 52.4, 51.8, 36.4, 31.4, 31.3, 25.3, 22.5, 14.5, 14.0; MS (CI, NH$_3$): m/z 246 [$M^+ + NH_4$], 229 [$M^+ + 1$].

(−)-Phaseolinic Acid (3)

A solution of **20** (20 mg, 0.09 mmol) and 6 N HCl (0.5 mL) in dioxane (1 mL) was refluxed for 2 h. The mixture was cooled and dioxane was evaporated. An acid/base treatment then furnished **3** as a white solid; yield: 17 mg (91 %); $[\alpha]_D^{20}$: −141 (*c* 0.25, CHCl$_3$), lit.[1c] $[\alpha]_D^{20}$: −150 (*c* 0.2, CHCl$_3$); ^{1}H NMR (400 MHz, CDCl$_3$): $\delta = 4.69$ (m, 1H), 3.21 (m, 1H), 3.04 (m, 1H), 1.57 (m, 2H), 1.31(d, 3H, $J = 7.1$ Hz), 1.43–1.24 (m, 6H), 0.90 (m, 3H); ^{13}C NMR (100 MHz, CDCl$_3$): $\delta = 177.5$, 176.3, 77.6, 51.5, 36.5, 31.4, 31.2, 25.4, 22.5, 14.5, 14.0.

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