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Diastereoselective total synthesis of (+)-morusimic acid B, an amino acid from *Morus alba*

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Abstract—An efficient, flexible and diastereoselective synthesis of the naturally occurring pyrrolidine amino acid, (+)-morusimic acid B, has been accomplished. Starting from chiral, optically active (+)-(3*S*)-hydroxy butyric acid methyl ester the key steps of our synthesis are diastereoselective α-alkylation of its dianion to introduce the main part of the side chain, Curtius rearrangement of the hydrazide derivative to a 2-oxazolidinone followed by $N\rightarrow\pi$-cyclization with mercury(II) acetate to generate the *cis*-2,5-disubstituted pyrrolidine ring. The remote C-3 stereocentre is established after chain elongation with the dianion of methyl acetoacetate and asymmetric hydrogenation of the resulting β-oxoester with Noyori's Ru(II)-(*R*)-BINAP catalyst.

1. Introduction

(+)-Morusimic acid B, (+)-(1″*S*,2′*S*,3*R*,5′*S*)-3-hydroxy-12-[5′-(1″-hydroxy-ethyl)-pyrrolidin-2′-yl]dodecanoic acid **1**, is an amino acid with a *cis*-2,5-disubstituted pyrrolidine ring as an amino function (Fig. 1). It was first isolated by Kusano et al. in 2002 from the ripened fruits of the white Mulberry tree (*Morus alba* L., Moracae) along with five new unknown nortropane alkaloids and five other new amino acids, morusimic acids A–F.[1] While morusimic acids A and B (B being the C-3-aglycone of morusimic acid A) are pyrrolidinyl dodecanoic acids, morusimic acids C–F contain a piperidin-3-ol ring as an amino moiety instead. In our continuing studies[2] in using enantiomerically pure, optical active β-hydroxyesters as starting materials for the syntheses of natural products with an α-aminohydroxy substructure we chose (+)-morusimic acid B as the target molecule particularly interested in diastereoselectively generating the *cis*-2,5-disubstituted pyrrolidine ring system. Furthermore, several compounds isolated from *M. alba* are known to show glycosidase inhibitory properties and are therefore of general pharmacological interest. Details of the single steps of our synthesis are described in the following (Scheme 1).

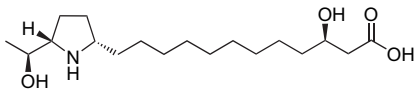

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Figure 1. (+)-Morusimic acid B.

Keywords: Pyrrolidine amino acid; (+)-Morusimic acid B; $N\rightarrow\pi$-Cyclization.
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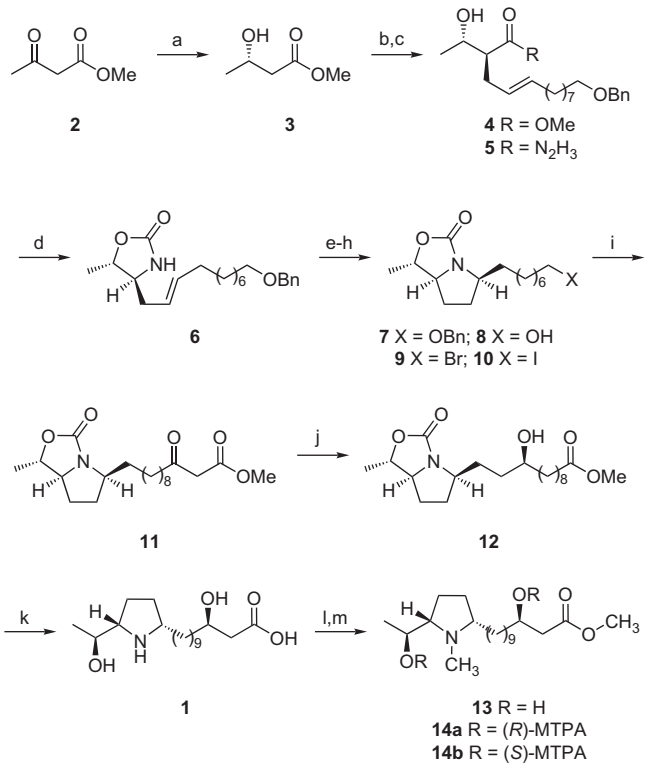
2. Synthesis

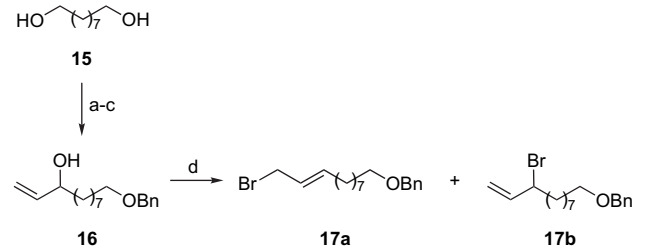
Starting from enantiopure (+)-(3*S*)-hydroxy butyric acid methyl ester **3** the later C-5′ stereocentre of (+)-morusimic acid B was introduced by diastereoselective *anti*-alkylation of the dianion with allyl bromide **17a**.[3] The ratio of *anti*/*syn*-products was determined by analysis of the ^{1}H NMR spectrum to be 96:4.

As an alkylating agent for the α-alkylation of β-hydroxyester **3** a 2:1-mixture of the allyl bromide isomers **17a** and **17b** was used to introduce the main part of the side chain as well as the required double bond for the $N\rightarrow\pi$-cyclization. These compounds were obtained starting from nonanediol. First the diol **15** was protected as monobenzyl ether using silver(I) oxide according to a procedure of Bouzide and Sauvé,[4] followed by Swern oxidation of the remaining alcohol function. Grignard addition of vinylmagnesium chloride to the crude aldehyde provided allylic alcohol **16**, which was transformed into the two isomeric allyl bromides **17a** and **17b** in a ratio of 2:1[5] by treatment with PBr_3.[6] The separation of these two isomers was not necessary since the dianion of **3** was only alkylated by primary allyl bromide **17a** (Scheme 2).

After separating the alkylation product from the remaining allyl bromide isomer **17b** by column chromatography the alkylated hydroxyester **4** was converted into hydrazide **5** by refluxing with hydrazine hydrate in methanol. Crystallizations of the crude hydrazide from EtOH twice removed the diastereomeric *syn*-byproduct and afforded pure (1′*S*,2*S*,4*E*)-**5** in 71% yield. Curtius rearrangement of **5** gave the *anti*-oxazolidinone **6** in quantitative yield with complete retention in configuration.[7] $N\rightarrow\pi$-Cyclization[8] by treatment of the



Scheme 1. Synthesis of (+)-(3*R*,2′*S*,5′*S*,1″*S*)-morusimic acid B **1** and the MTPA esters **14a** and **14b**. Reagents and conditions: (a) H_2 (5 bar), 0.1 mol % Ru(II)-(−)-(*S*)-BINAP, MeOH, 85 °C, 60 h, 91.5%; (b) 2.2 equiv LiHMDS, 1.5 equiv DMPU, 1.5 equiv **17a**, THF, −78 °C→rt, cc, 65%; (c) 10 equiv $N_2H_4\cdot H_2O$, cat. DMAP, MeOH, reflux, 120 °C, 24 h, recryst, 71%; (d) 6 N HCl, 2.75 equiv $NaNO_2$, MeOH/H_2O, 15 h, 0 °C→rt; (e) 3 equiv $Hg(OAc)_2$, 1:1 THF/H_2O, 15 h, rt, then 1 M $NaBH_4$ in 3 M NaOH, cc, 74% over two steps; (f) Pd/C, H_2 (1 atm), MeOH, rt, 3 h, 100%; (g) 1.3 equiv PPh_3, 1.3 equiv CBr_4, THF/CH_3CN, 0 °C→rt, 2.5 h, cc, 98%; (h) 3 equiv NaI, acetone, rt, 16 h, cc, 99%; (i) 0.3 equiv 10, 1 equiv **2**, 1.25 equiv NaH, 1.25 equiv *n*-BuLi, THF, −5 °C→18 °C, cc, 65%; (j) H_2 (5 bar), 3.2 mol % Ru(II)-(+)-(*R*)-BINAP, MeOH, 70 °C, 24 h, cc, 90%; (k) 6 equiv $Ba(OH)_2\cdot 8H_2O$, dioxane/H_2O, reflux, 110 °C, 24 h, recryst, 91%; (l) CH_2N_2, MeOH/Et_2O, 16 h, rt, cc, 70%; (m) 2.4 equiv (*S*)-(+)-MTPA-Cl, and (*R*)-(−)-MTPA-Cl, respectively 5 equiv Et_3N, cat. DMAP, DCM, rt, 60 min, cc, 80.4%, and 72.8%, respectively; 16% overall yield of **1**.



Scheme 2. Synthesis of the central part of the side chain. Reagents and conditions: (a) 1.5 equiv Ag_2O, 1.1 equiv BnBr, DCM, rt, 16 h, cc; (b) 1.1 equiv $(COCl)_2$, 2.2 equiv DMSO, 5 equiv NEt_3, DCM, −78 °C→0 °C; (c) 1.4 equiv vinylMgCl, THF, −30 °C→−5 °C→rt, 2 h, cc, 51.8% over three steps; (d) 0.4 equiv PBr_3, 0.15 equiv pyridine, PE, −25 °C→−5 °C, 40 min, −5 °C→rt, 80 min, cc, 56% of **17a**, 28% of **17b**; 29% overall yield of **17a** over four steps.

crude oxazolidinone **6** with mercury(II) acetate in a water/THF suspension provided the required 2,5-disubstituted pyrrolidine ring incorporated into the bicyclic oxazolone **7**. The reaction was found to be highly diastereoselective since no signals of the diastereoisomer could be observed in the ^1H and ^{13}C NMR spectra of crude **7**. To determine the absolute stereochemistry of the newly formed stereocentre at C-5 NOE measurements on the bicyclic system were performed (Fig. 2). Due to these NOE experiments the $N\rightarrow\pi$-cyclization led to the desired (5*S*)-*endo*-epimer **7** with a de >99%. The detected NOE between H-5 and H-7a as well as the absence of a NOE between H-1 and H-5 unambiguously proved the *endo*-stereochemistry as well as the absolute configuration of the bicycle. It is likely that the diastereoselective formation of a cyclic mercuronium intermediate and the S_N2-type opening of the mercura cycle after bond rotation brings the side chain into the sterically unfavoured *endo*-position. Interestingly, the length of the side chain of **6** was found to be responsible for the high diastereoselectivity since analogue compounds[9] of **6** with *shorter* side chains also led to larger amounts of the (5*R*)-*exo*-epimers (Table 1). These (5*R*)-*exo*-epimers showed NOE signals between H-1 and H-5 as discussed above (Fig. 2).

To complete the carbon scaffold compound **7** was deprotected by treatment with Pd/C/H_2 to give alcohol **8**, which in turn was transformed via bromide **9**[10] into iodide **10** (97% yield over three steps). According to the general procedure of Weiler[11] iodide **10** was coupled with the dianion of methyl acetoacetate **2** forming the β-oxo methyl ester **11** in 65% yield. The diastereoselective hydrogenation of β-oxo methyl ester **11** using Noyori's procedure[12] with (*R*)-BINAP-ruthenium as chiral catalyst led to the desired (3*R*)-hydroxy methyl ester **12** in 90% yield and an excellent de>99% according to NMR measurements. In the final step of the synthesis compound **12** was saponified by refluxing with a suspension of barium hydroxide in a water/1,4-dioxane-mixture for 24 h. In the course of saponification the oxazolidinone ring and the methyl ester were cleaved simultaneously to provide the amino acid carboxylate. Neutralization with 2 N sulfuric acid adjusting pH 6, filtration and recrystallization from MeOH finally afforded (+)-morusimic acid B (**1**) in its betain form (Fig. 3) in 91% yield.

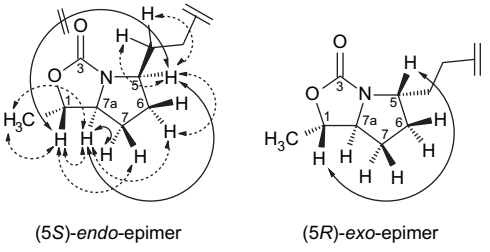
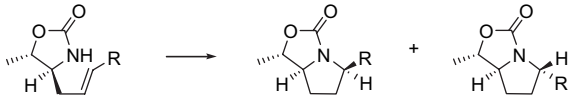


Figure 2. NOEs detected on the bicyclic system.

Table 1. Stereochemical effect of the chain length on the stereoselectivity of the $N\rightarrow\pi$-cyclization



	(5*S*)-*endo*-epimer (%)	(5*R*)-*exo*-epimer (%)
R=propyl[7]	82	18
R=octyl[7]	96	4
R=8′-BnO-octyl	>99	1

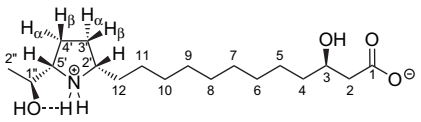


Figure 3. Betain structure of (+)-morusimic acid B at pH 6–7.

To confirm the (3*R*)-configuration of synthesized morusimic acid B a modification of Mosher's method[13] was applied. For this purpose, synthesized **1** was initially treated with an ethereal solution of diazomethane[14] in excess to obtain the methyl ester. Surprisingly co-methylation of the amino group occurred at the same time giving (+)-*N*-methyl morusimic acid B methyl ester **13** in one step in 70% yield. Subsequent esterification with (*R*)-(−)- and (*S*)-(+)-MTPA-chloride afforded the Mosher esters **14a** and **14b** in 80.4% and 89.2% yield, respectively.

3. Results and discussion

Our stereochemically precise synthesis leads to a product featuring the stereochemistry for (+)-morusimic acid B as proposed by Kusano et al.[1] However, the ^{1}H and ^{13}C NMR spectra of our synthesized product show noteworthy deviations from the data published in Ref. 1. We discovered that the chemical shifts in the ^{1}H and ^{13}C NMR spectra are highly pH-dependent. To quantify these effects we measured a sequence of samples with an accurately defined pH value. The NMR samples for these measurements were prepared by stepwise acidification with trifluoro acetic acid starting from a basic aqueous solution of the sodium carboxylate of (+)-morusimic acid B under control with a pH metre. The largest observed differences for the chemical shifts between the morusimic acid B carboxylate anion at pH 14 and the related pyrrolidinium cation at pH 1 are up to 0.6 ppm in ^{1}H NMR and 4.45 ppm in the ^{13}C NMR shifts (see Table 2).

According to these NMR experiments and the observed shifts the amino group is protonated first during the addition of the acid, being a stronger base than the carboxylate group. Between pH 6 and 7 morusimic acid B exists in its neutral betain form (Fig. 3).

As we anticipated the most significant differences among the ^{13}C NMR chemical shifts are at C-1 of the carboxylate group with a $\Delta\delta$=4.45 ppm as well as at the carbons C-12 and C-1″ flanking the pyrrolidine ring with $\Delta\delta$=3.98 ppm and $\Delta\delta$=2.87 ppm, respectively. Thus, we conclude that especially the ^{13}C NMR data are of limited diagnostic value for a structural comparison between our synthesized compound and the natural product as characterized by Kusano et al.[1] in 2002.

Since these pH-dependent NMR measurements caused uncertainties we decided to do further analyses to unambiguously verify the stereochemistry of our synthesized product. Additional NOE experiments were carried out on **1**[15] to confirm the relative and consequently the absolute stereochemistries of the pyrrolidine moiety of synthesized (+)-morusimic acid B. The detected NOEs on **1** are shown in Figure 4.

Table 2. ^{1}H and ^{13}C NMR spectral data for morusimic acid B at various pH values

Proton	pH 14	pH 7	pH 6	pH 5	pH 1	pH 1−pH 14	Lit. 1
2a	2.22	2.22	2.23	2.30	2.41	0.19	2.26
2b	2.34	2.35	2.36	2.41	2.51	0.17	2.32
3	3.88	3.89	3.89	3.93	3.99	0.11	3.98
4	n/a	1.46	1.46	1.47	1.50	n/a	1.46
5–11	1.22–1.60	1.25–1.42	1.27–1.42	1.27–1.43	1.28–1.45	0.06–0.29	1.30–1.49
12, 3α′, 4α′		1.52–1.78	1.62–1.88	1.62–1.88	1.63–1.89		1.64 and 1.75
2′	2.96	3.29	3.50	3.50	3.52	0.56	3.45
3β′	1.90	2.11	2.24	2.24	2.25	0.35	2.15
4β′	1.78	1.99	2.13	2.13	2.14	0.36	2.01
5′	2.87	3.21	3.43	3.43	3.44	0.57	3.43
1″	3.56	3.75	3.87	3.86	3.88	0.32	3.88
2″	1.16	1.21	1.24	1.24	1.25	0.09	1.22

Carbon	pH 14	pH 7	pH 6	pH 5	pH 1	pH 14−pH 1	Lit. 1
1	181.11	181.37	181.37	179.44	176.66	4.45	180.94
2	45.41	45.47	45.46	44.54	43.04	2.37	45.62
3	70.28	69.88	70.41	69.99	69.36	0.92	70.61
4	38.18	38.23	38.24	38.18	38.13	0.05	38.18
5	26.72	26.74	26.73	26.69	26.66	0.06	26.75
6–10	30.62, 30.65, 30.69, 30.79, 30.87	30.51, 30.57, 30.61, 30.67, 30.78	30.39, 30.40, 30.51, 30.63, 30.75	30.39, 30.40, 30.51, 30.62, 30.70	30.40, 30.41, 30.53, 30.62, 30.63	0.22–0.24	30.51, 30.59, 30.65, 30.71, 30.78
11	28.63	28.07	27.72	27.72	27.72	0.91	28.25
12	37.10	34.74	33.17	33.12	33.12	3.98	36.08
2′	60.43	61.33	61.87	61.91	61.96	−1.53	62.29
3′	32.12	31.01	30.26	30.24	30.23	1.89	31.73
4′	28.43	27.56	26.82	26.79	26.80	1.63	27.41
5′	66.34	67.06	67.51	67.54	67.56	−1.22	66.22
1″	71.51	70.41	68.67	68.61	68.67	2.87	67.07
2″	21.34	21.18	21.10	21.12	21.11	0.23	21.30

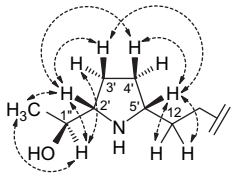


Figure 4. NOEs detected on the pyrrolidine moiety of (+)-morusimic acid B.

The detected NOEs on the pyrrolidine moiety of **1** prove once more the (2′*S*,5′*S*)-cis-configuration of the pyrrolidine ring in the target molecule. As specified before the absolute stereochemistry at C-1″ and C-5′ in the synthesis had been obtained by the stereoselective *anti*-addition of bromide **17a** to enantiomerically pure (+)-(3*S*)-hydroxy butyric acid methyl ester **3** leading to the *anti*-configuration in oxazolidinone **6**. The stereoselective $N\rightarrow\pi$-cyclization of oxazolidinone **6** finally created the pyrrolidine ring and the third stereocentre at C-2′ with *S*-configuration (Scheme 3, see Figs. 2 and 4 for NOEs detected on **1** as well as its precursors **7**–**10**).

To verify the (3*R*)-configuration of synthesized (+)-morusimic acid B obtained by the stereoselective (*R*)-BINAP-Ru(II) catalyzed Noyori's reduction of **11** a modification of Mosher's method[13] was applied. The results are shown in Figure 5.

The analysis of the spectral data for the MTPA esters **14a** and **14b** according to the Mosher's protocol[13] (Fig. 5) corresponds perfectly with the published data[1] for the β-hydroxy carboxylic moiety of the molecule and proves the configuration at C-3 to be *R*. Additionally, the *S*-configuration at C-1″ was once more confirmed. In conclusion the absolute configuration of synthesized **1** is 3*R*,2′*S*,5′*S*,1″*S* beyond doubt. Nevertheless, it should be noted that the calculated $\Delta\delta$ values of the pyrrolidine moiety slightly differ from the results reported in Ref. 1. As we already pointed out before the ^{1}H und ^{13}C chemical shifts of the pyrrolidine moiety are very sensitive to changes of the pH value. Thus, it is most evident that the observed differences result from pH variations in the NMR samples.

We fully agree with the structural assignment of (+)-morusimic acid B by Kusano et al.[1] Since our independent stereochemical analyses lead to the same results, we conclude that our synthesized compound and the natural product are identical. This conclusion is supported by the comparison of the specific rotation of natural (+)-morusimic acid B[1] and the synthesized compound (see Table 3). The specific rotation of synthesized morusimic acid B deviates from the natural product by only 0.47° (5.3%), which is within experimental error. A comparison by the melting point is not possible since it has not been published for the natural product.

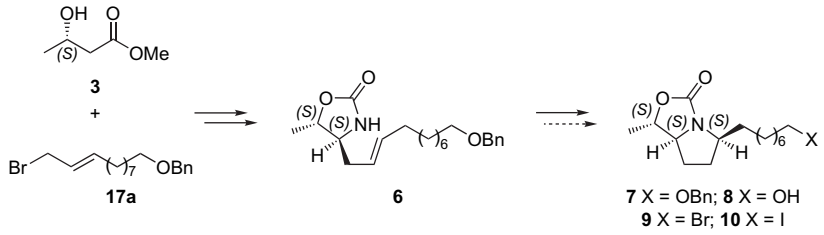
Table 3. Specific rotations and melting points of natural occurring and synthesized morusimic acid B

Natural morusimic acid B isolated by Kusano et al.	Synthetic morusimic acid B (betain form, pH 6–7)
$[\alpha]_D^{20}$ +8.8 (*c* 0.42, MeOH) mp not given	$[\alpha]_D^{20}$ +8.33 (*c* 0.42, MeOH) mp: 172±2 °C (decomposition)

4. Conclusion

In summary, the naturally occurring amino acid (+)-morusimic acid B was synthesized in a 10-steps sequence with high purity and an excellent overall yield of 17.3% based on the optically active (+)-(3*S*)-hydroxyester **3**. All reactions are highly diastereoselective and can be easily carried out on a multigram scale. Gram quantities of this optically active amino acid are now available for further pharmacological studies.[16] Since both enantiomers of the starting material are accessible, the presented synthesis allows access to the unnatural enantiomer, (−)-morusimic acid B (−)-(1″*R*,2′*R*,3*S*,5′*R*)-**1**, as well as to the C-3 epimers.

Note added in proof: A referee has questioned the identity of our synthesized compound **1** with that of the natural product as described by Kusano et al.[1] To this the following should be noted. This work is based on 300 mg of synthesized **1** (rather than 25 mg of the isolated natural product as in Ref. 1). Our pH-dependent ^{1}H and ^{13}C NMR data are



Scheme 3. Stereoselective formation of the (2′*S*,5′*S*)-*cis*-pyrrolidine ring of (+)-morusimic acid B.

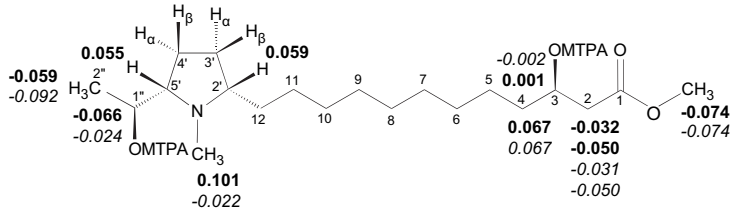


Figure 5. Δδ values [**14b**(*S*)−**14a**(*R*)] obtained for the MTPA esters (bold). Published data from Ref. 1 is in italic.

especially sensitive in the region of the (protonated) nitrogen of the pyrrolidine moiety i.e., C-1″ and C-12 flanking the pyrrolidine ring. The surprising N-methylation of **1** with diazomethane (**1**→**13**) is in accord with the zwitterion formulation containing an acidic N–H proton (see Fig. 3).

5. Experimental section

5.1. General

Air- and/or moisture sensitive reactions were carried out in dried glassware under a positive pressure of nitrogen. Commercially available materials were obtained from Aldrich, Fluka, Lancaster, Merck or Acros, and used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium wire/benzophonone, dichloromethane was distilled from CaH_2. Triethylamine (NEt_3) and pyridine were distilled and stored over KOH, dimethyl sulfoxide (DMSO) was stored over 4 Å molecular sieves. Methanol and dimethylformamide (DMF) were degassed via three consecutive freeze-thaw cycles. Column chromatography was performed on silica gel 60 from Macherey Nagel (40–63 μm) using mixtures of *n*-hexane, ethyl acetate (EtOAc), MTB ether and methanol (MeOH). ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-400 and AVS-400 spectrometers with tetramethylsilane as an internal standard, respectively. Overlapping signals are marked with an asterisk (*). ^{13}C NMR spectra were measured with the APT and DEPT techniques. IR spectra were recorded with the Bruker fourier transformation IR spectrometers Vector 22 and Tensor 37 by the ATR method, respectively. Mass spectra (EI) were obtained with a Finnigan MAT 312 instrument and a VG Autospec (high resolution), electro spray mass spectrometry (ESI) was performed with a Waters Micromass LCT. Melting points were measured in an Electrothermal IA9200 digital melting point apparatus or a Tottoli apparatus Büchi 510 and are uncorrected. Optical rotation power was determined with a Perkin–Elmer 241 polarimetre at room temperature at a wavelength of 589.3 nm (sodium lamp) using a 1 mL quartz cell.

5.1.1. (+)-(3*S*)-3-Hydroxy butyric acid methyl ester (3). $[RuCl_2(p\text{-cymene})]_2$ (459 mg, 0.75 mmol) and (*S*)-(−)-BINAP (933 mg, 1.5 mmol) were dissolved in degassed DMF (30 mL) and stirred at 105 °C for 25 min under an atmosphere of nitrogen. Then the DMF was removed in vacuo to yield a dark red solid. A solution of methyl acetoacetate **2** (174 g, 1.5 mol) in 250 mL of degassed methanol was added to the solid catalyst and this mixture was transferred to the hydrogenation reactor via flexible needle. The solution was then treated with hydrogen (5 bar) at 85 °C under stirring for 60 h. After cooling to room temperature the methanol was removed under reduced pressure. The crude product was purified by distillation at 5 mbar (bp 45–48 °C) affording 162 g (1.37 mol, 91.5%) of β-hydroxyester **3** as colourless liquid.

^1H NMR (400 MHz, $CDCl_3$): δ=1.23 (d, J=6 Hz, 3H, H_3C-4), 2.44 (dd, J_1=16.4 Hz, J_2=8 Hz, 1H, H_aC-2), 2.50 (dd, J_1=16.4 Hz, J_2=3.8 Hz, 1H, H_bC-2), 3.01 (br, 1H, OH), 3.72 (s, 3H, OCH_3), 4.20 (ddq, J_1=8 Hz, J_2=3.8 Hz, J_3=6 Hz, 1H, HC-3).

^{13}C NMR (100 Hz, $CDCl_3$): δ=22.50 (H_3C-4), 42.65 (H_2C-2), 51.73 (OCH_3), 64.26 (HC-3), 173.30 (OC-1).

IR (Golden Gate ATR): $\tilde{\nu}$=3435 (b) [O–H], 2973 (m), 2362 (w), 2342 (w), 2082 (w), 1722 (s) [C=O], 1438 (s), 1410 (m), 1376 (m), 1293 (s), 1257 (m), 1193 (s), 1171 (vs), 1123 (s), 1069 (s), 1005 (s), 944 (s), 884 (w), 851 (m), 719 (w), 669 (w) cm^{-1}.

EI-MS: m/z=119 ($[M+H]^+$, 19.5%), 118 (M^+, 3.5%), 59 (100%). HRMS (EI): calcd for $C_5H_{10}O_3$: 118.062994; found: 118.062918.

$[\alpha]_D^{20}$ +50.66 (*c* 1.83, $CHCl_3$).

5.1.2. (−)-(1′*S*,2*S*,4*E*)-13-Benzyloxy-2-(1′-hydroxyethyl)-tridec-4-enoic acid methyl ester (4). To 148 mL (148 mmol, 2.2 equiv) of LiHMDS solution (1 M in THF) was added dropwise the solution of (+)-(3*S*)-hydroxy butyric acid methyl ester **3** (7.87 g, 66.7 mmol, 1 equiv) in dry THF (15 mL) under nitrogen, the mixture being allowed to warm from −70 to −60 °C. Immediately after the addition of the ester dry DMPU (12.82 g, 100 mmol, 1.5 equiv) was added in one portion. After additional stirring for 30 min at −60 °C the mixture was recooled to −70 °C and 51 g of a 2:1-mixture of (2*E*)-11-benzyloxy-1-bromo-undec-2-en **17a** (100 mmol, 1.5 equiv) and 11-benzyloxy-3-bromo-undec-1-en **17b** (50 mmol, 0.75 equiv) (see Section 5.1.15) were added dropwise below −65 °C. The reaction mixture was then allowed to warm to 0 °C over 4 h. Then the mixture was quenched with 100 mL of 1 M citric acid and H_2O (100 mL) at 0 °C adjusting to a pH of 6. After evaporation of the THF the aqueous residue was extracted three times with EtOAc. The combined organic extracts were dried over Na_2SO_4 and evaporated in vacuo to afford the crude alkylation product and the remaining excess allyl bromides as dark orange oil, which were separated by column chromatography. The diastereomeric ratio of the *anti*/*syn* products was determined by ^1H NMR spectroscopy to be 96:4 in favour for the desired (2*S*)-*anti* epimer **4**.

^1H NMR (400 MHz, $CDCl_3$): δ=1.19–1.40* (br m, 10H, H_2C-7 and H_2C-11), 1.21* (d, J=6.5 Hz, 3H, H_3C-2′), 1.60 (apparent quin, J=7 Hz, 2H, H_2C-12), 1.95 (apparent q, J=6.7 Hz, 2H, H_2C-6), 2.32 (dd, J_1=J_2=6.8 Hz, 2H, H_2C-3), 2.43 (dt, J_1=6.7 Hz, J_2=6.7 Hz, 1H, HC-2), 2.69 (br, 1H, OH), 3.45 (t, J=6.7 Hz, 2H, H_2C-13), 3.68 (s, 3H, OCH_3), 3.91 (quin, J=6.3 Hz, 1H, HC-1′), 4.94 (s, 2H, $OCH_2C_6H_5$), 5.31 (dt, J_1=15 Hz, J_2=7 Hz, 1H, HC-4), 5.48 (dt, J_1=15 Hz, J_2=6.8 Hz, 1H, HC-5), 7.22–7.36 (m, 5H, Ar–CH).

^{13}C NMR (100 Hz, $CDCl_3$): δ=21.40 (H_3C-2′), 26.18, 29.02, 29.38, 29.41, 29.42, 29.75 (6×CH_2, H_2C-7–H_2C-12), 32.47 (2×CH_2, H_2C-3 and H_2C-6), 51.48 (OCH_3), 52.86 (HC-2), 67.79 (HC-1′), 70.48 (H_2C-13), 72.83 ($OCH_2C_6H_5$), 125.83 (HC-4), 127.44, 127.60, 128.32 (5×CH, Ar–CH), 133.52 (HC-5), 138.69 (Ar–C_q), 175.33 (OC-1).

IR (Golden Gate ATR) $\tilde{\nu}$=3447 (b) [O–H], 3030 (w), 2926 (s), 2853 (s), 1736 (vs) [C=O], 1496 (w), 1454 (m), 1437 (s), 1364 (m), 1270 (m), 1270 (m), 1198 (s), 1168 (s), 1098 (vs), 1028 (m), 968 (s), 944 (m), 877 (w), 846 (w), 735 (s), 697 (vs), 612 (w) cm^{-1}.

EI-MS: *m*/*z*=377 ([M+H]$^+$, 51.1%), 376 (M$^+$, 22.4%), 81 (100%). HRMS (EI): calcd for $C_{23}H_{36}O_4$: 376.261360; found: 376.261322. HRMS (ESI): calcd for $C_{23}H_{36}O_4Na$ [M+Na]$^+$: 399.2511; found: 399.2506.

$[\alpha]_D^{20}$ (96:4 *anti*/*syn* mixture) −4.2 (*c* 1.02, $CHCl_3$).

5.1.3. (−)-(1′*S*,2*S*,4*E*)-13-Benzyloxy-2-(1′-hydroxy-ethyl)-tridec-4-enoic acid hydrazide (5). The 96:4 *anti*/*syn* mixture of ester **4** (20.7 g, 55 mmol, 1 equiv) was dissolved in MeOH (55 mL), treated with hydrazine hydrate (27.5 g, 550 mmol, 10 equiv) and 4-(dimethylamino)-pyridine (DMAP) (443 mg, 3.63 mmol) and refluxed at 115 °C for 24 h. Then the solvent and volatile components of the mixture were evaporated under reduced pressure, residues of hydrazine hydrate were removed by suspending the crude hydrazide in 50 mL water and drying in high vacuum. The remaining light yellow solid was purified by recrystallization (three times) from EtOH affording 14.71 g (39 mmol, 71%) of bright white, pure hydrazide **5** free from the *syn*-epimer.

^{1}H NMR (400 MHz, CD_3OD): δ=1.18 (d, *J*=6.5 Hz, 3H, H_3C-2′), 1.22–1.41 (br m, 10H, H_2C-7 and H_2C-11), 1.59 (apparent quin, *J*=7 Hz, 2H, H_2C-12), 1.96 (apparent q, *J*=6.7 Hz, 2H, H_2C-6), 2.06–2.29 (m, 3H, HC-2 and H_2C-3), 3.47 (t, *J*=6.5 Hz, 2H, H_2C-13), 3.84 (quin, *J*=6.7 Hz, 1H, HC-1′), 4.48 (s, 2H, $OCH_2C_6H_5$), 5.32 (dt, J_1=15 Hz, J_2=6.8 Hz, 1H, HC-4), 5.47 (dt, J_1=15 Hz, J_2=6.7 Hz, 1H, HC-5), 7.23–7.36 (m, 5H, Ar–CH).

^{13}C NMR (100 Hz, CD_3OD): δ=21.58 (H_3C-2′), 27.28, 30.19, 30.51, 30.57, 30.60, 30.75 (6×CH_2, H_2C-7–H_2C-12), 33.25, 33.61 (H_2C-3 and H_2C-6), 54.24 (HC-2), 69.16 (HC-1′), 71.45 (H_2C-13), 73.88 ($OCH_2C_6H_5$), 127.88 (HC-4), 128.65, 128.87, 129.38 (5×CH, Ar–CH), 134.01 (HC-5), 139.89 (Ar–C_q), 175.91 (OC-1).

IR (Golden Gate ATR): $\tilde{\nu}$=3282 (s) [N–H], 3034 (w), 2922 (s), 2851 (s), 1646 (vs) [C═O], 1619 (s), 1531 (s), 1496 (w), 1454 (m), 1430 (m), 1367 (m), 1339 (m), 1267 (m), 1209 (w), 1120 (s), 1099 (vs), 1029 (m), 963 (vs), 934 (s), 773 (w), 733 (s), 695 (s), 675 (s), 612 (w) cm^{-1}.

EI-MS: *m*/*z*=377 ([M+H]$^+$, 9.25%), 376 (M$^+$, 8.5%), 91 (100%). HRMS (EI): calcd for $C_{22}H_{36}N_2O_3$: 376.272593; found: 376.273061. HRMS (ESI): calcd for $C_{22}H_{36}N_2O_3Na$ [M+Na]$^+$: 399.2624; found: 399.2620.

$[\alpha]_D^{20}$ −7.1 (*c* 1.0, MeOH); mp: 139 °C.

5.1.4. (−)-(2′*E*,4*S*,5*S*)-4-(11′-Benzyloxy-undec-2-enyl)-5-methyl-oxazolidin-2-one (6). To the solution of hydrazide **5** (15 g, 40 mmol, 1 equiv) in MeOH (150 mL) was added slowly 40 mL (240 mmol, 6 equiv) of 6 N HCl under magnetic stirring at 0 °C. Then the solution of sodium nitrite (7.6 g, 110 mmol, 2.75 equiv) in 60 mL of water was added dropwise at the same temperature. This mixture was stirred at 0 °C for further 30 min and then overnight (15 h) at room temperature. After recooling to 0 °C the reaction mixture was neutralized by addition of 2 N NaOH (approx. 70 mL) adjusting to a pH of 5–6. The organic solvent was evaporated and the aqueous residue was extracted four times with EtOAc. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo to yield 14.5 g of crude oxazolidinone **6** as an yellow oil, which was used in the next step without further purification. A small amount was purified by column chromatography to obtain an analytical sample.

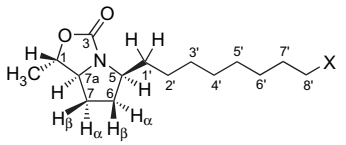
^{1}H NMR (400 MHz, $CDCl_3$): δ=1.21–1.41* (br m, 10H, H_2C-5′–H_2C-9′), 1.38* (d, *J*=6.3 Hz, 3H, H_3C–C-5), 1.61 (apparent quin, *J*=7 Hz, 2H, H_2C-10′), 2.00 (apparent q, *J*=6.9 Hz, 2H, H_2C-4′), 2.22 (t, *J*=6.7 Hz, 2H, H_2C-1′), 3.38 (q, *J*=6.3 Hz, 1H, HC-4), 3.46 (t, *J*=6.6 Hz, 2H, H_2C-11′), 4.30 (quin, *J*=6.1 Hz, 1H, HC-5), 4.50 (s, 2H, $OCH_2C_6H_5$), 5.28 (dt, J_1=15 Hz, J_2=7.1 Hz, 1H, HC-2′), 5.55 (dt, J_1=15 Hz, J_2=6.9 Hz, 1H, HC-3′), 6.15 (s, 1H, NH), 7.23–7.38 (m, 5H, Ar–CH).

^{13}C NMR (100 Hz, $CDCl_3$): δ=20.26 (H_3C–C-5), 26.17, 29.10, 29.66, 29.39, 29.41, 29.75 (6×CH_2, H_2C-5′–H_2C-10′), 32.59 (H_2C-4′), 37.98 (H_2C-1′), 59.19 (HC-4), 70.49 (H_2C-11′), 72.83 ($OCH_2C_6H_5$), 78.20 (HC-5), 123.26 (HC-2′), 127.46, 127.61, 128.32 (5×CH, Ar–CH), 135.72 (HC-3′), 138.66 (Ar–C_q), 159.20 (OC-2).

IR (Golden Gate ATR): $\tilde{\nu}$=3270 (b), 2925 (m), 2853 (m), 1747 (vs) [C═O], 1496 (w), 1454 (w), 1384 (m), 1235 (m), 1099 (m), 1054 (m), 971 (m), 906 (w), 770 (w), 734 (m), 967 (s), 612 (w) cm^{-1}.

EI-MS: *m*/*z*=360 ([M+H]$^+$, 11.1%), 359 (M$^+$, 6.8%), 91 (100%). HRMS (EI): calcd for $C_{22}H_{33}NO_3$: 359.246044; found: 376.245911. HRMS (ESI): calcd for $C_{22}H_{33}NO_3Na$ [M+Na]$^+$: 382.2358; found: 382.2357.

$[\alpha]_D^{20}$ −26.5 (*c* 1.03, $CHCl_3$).



7: X = OBn; **8**: X = OH;
9: X = Br; **10**: X = I

5.1.5. (+)-(1*S*,5*S*,7a*S*)-5-(8′-Benzyloxy-octyl)-1-methyl-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one (7). Mercuric acetate (31.87 g, 100 mmol, 3 equiv) was placed in a 2000-mL round bottom flask and suspended in the 1:1 mixture of H_2O (330 mL) and THF (330 mL). To this vigorously stirred suspension a solution of crude oxazolidinone **6** (11.8 g, 32.8 mmol, 1 equiv) in THF (110 mL) was added dropwise. The orange suspension was stirred overnight at room temperature (15 h). Then the alkyl mercurial formed was reduced with excess sodium borohydride solution (164 mL, 1 M $NaBH_4$ in 3 M NaOH) at 0 °C. After additional stirring for 30 min at room temperature the THF was removed in vacuo and the aqueous residue was extracted with MTB ether (four times). During the extraction the metallic mercury coalesced over the outlet of the separating funnel and could easily be removed. The organic extracts were dried over Na_2SO_4 and concentrated in vacuo, leaving the crude product, which was subjected to column chromatography (∅ 8 cm×10 cm, EtOAc/*n*-hexane, 1:10–1:7) affording 8.7 g (24.2 mmol) of **7** as colourless oil (74% over two steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.20–1.40* (br m, 10H, H_2C-2′–H_2C-6′), 1.42* (d, J=6.1 Hz, 3H, H_3C–C-1), 1.42* (m, 1H, H_bC-1′), 1.50–1.64 (m, 3H, H_βC-7 and H_2C-7′), 1.91 (m, 2H, H_βC-6 and H_αC-7), 2.14 (m, 1H, H_αC-6), 2.28 (m, 1H, H_aC-1′), 3.46* (t, J=6.6 Hz, 2H, H_2C-8′), 3.50* (dddd, J_1=J_2=3.5 Hz, J_3=7.9 Hz, J_4=9.2 Hz, 1H, HC-5), 3.71 (ddd, J_1=9.1 Hz, J_2=8.2 Hz, J_3=5.8 Hz, 1H, HC-7a), 4.29 (dq, J_1=8.1 Hz, J_2=6.2 Hz, 1H, HC-1), 4.50 (s, 2H, O$CH_2C_6H_5$), 7.22–7.36 (m, 5H, Ar–CH).

^{13}C NMR (100 Hz, $CDCl_3$): δ=19.18 (H_3C–C-1), 26.12 (H_2C-6′), 26.63 (H_2C-2′), 27.98 (H_2C-7), 29.37, 29.47, 29.49 (3×CH_2, H_2C-3′–H_2C-5′), 29.72 (H_2C-7′), 30.52 (H_2C-1′), 33.43 (H_2C-6), 56.42 (HC-5), 67.79 (HC-7a), 70.47 (H_2C-8′), 72.82 (O$CH_2C_6H_5$), 78.74 (HC-1), 127.42, 127.58, 128.31 (5×CH, Ar–CH), 138.68 (Ar–C_q), 156.01 (OC-3).

IR (Golden Gate ATR): $\tilde{\nu}$=2926 (m), 2854 (m), 1745 (vs) [C═O], 1496 (w), 1454 (m), 1407 (w), 1384 (m), 1361 (m), 1260 (m), 1205 (w), 1099 (s), 1047 (m), 906 (w), 800 (w), 764 (s), 736 (m), 698 (s), 649 (w), 612 (w) cm^{-1}.

EI-MS: m/z=359 (M^+, 3%), 91 (100%). HRMS (EI): calcd for $C_{22}H_{33}NO_3$: 359.246044; found: 376.245941. HRMS (ESI): calcd for $C_{22}H_{34}NO_3$: 360.2539; found: 360.2553. calcd for $C_{22}H_{33}NO_3Na$ $[M+Na]^+$: 382.2358; found: 382.2364.

$[\alpha]_D^{20}$ +16.4 (c 1.06, $CHCl_3$).

5.1.6. (+)-(1*S*,5*S*,7a*S*)-5-(8′-Hydroxy-octyl)-1-methyl-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one (8). Tetrahydro-oxazolone **7** (2.5 g, 7 mmol) was dissolved in MeOH (30 mL) under magnetic stirring and hydrogenated over 150 mg of Pd/C (10%) at atmospheric pressure for 3 h. Filtration over a short column of SiO_2 and evaporation of the solvent yielded 1.89 g (7 mmol, 100%) of alcohol **8** as colourless oil that crystallized in the refrigerator to a white solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.21–1.39* (br s, 10H, H_2C-2′–H_2C-6′), 1.43* (d, J=6.1 Hz, 3H, H_3C–C-1), 1.43* (m, 1H, H_bC-1′), 1.52–1.63 (m, 3H, H_2C-7′ and H_βC-7), 1.93 (m, 2H, H_βC-6 and H_αC-7), 2.00 (br, 1H, OH), 2.15 (m, 1H, H_αC-6), 2.26 (m, 1H, H_aC-1′), 3.51 (dddd, J_1=J_2=3.8 Hz, J_3=7.7 Hz, J_4=9.2 Hz, 1H, HC-5), 3.62 (t, J=6.6 Hz, 2H, H_2C-8′), 3.73 (ddd, J_1=J_2=8.6 Hz, J_3=5.5 Hz, 1H, HC-7a), 4.31 (dq, J_1=8.1 Hz, J_2=6.2 Hz, 1H, HC-1).

^{13}C NMR (100 Hz, $CDCl_3$): δ=19.59 (H_3C–C-1), 25.68 (H_2C-2′), 26.55 (H_2C-6′), 28.00 (H_2C-7), 29.28, 29.42, 29.44, (3×CH_2, H_2C-3′–H_2C-5′), 30.51 (H_2C-1′), 32.72 (H_2C-7′), 33.47 (H_2C-6), 56.43 (HC-5), 62.84 (H_2C-8′), 67.84 (HC-7a), 78.83 (HC-1), 156.11 (OC-3).

IR (Golden Gate ATR): $\tilde{\nu}$=3449 (m), 2910 (m), 2852 (m), 1704 (vs) [C═O], 1467 (m), 1451 (m), 1410 (m), 1387 (s), 1348 (m), 1314 (m), 1279 (m), 1220 (w), 1161 (m), 1143 (w), 1091 (m), 1074 (m), 1058 (m), 1042 (m), 1026 (s), 1010 (m), 995 (m), 955 (m), 941 (m), 907 (w), 892 (m), 805 (w), 772 (s), 725 (w), 676 (m), 653 (w) cm^{-1}.

EI-MS: m/z=270 ($M+H^+$, 8.2%), 269 (M^+, 18.4%), 140 (100%). HRMS (EI): calcd for $C_{15}H_{27}NO_3$: 269.199094; found: 269.199188. HRMS (ESI): calcd for $C_{15}H_{28}NO_3$: 270.2069; found: 270.2074.

$[\alpha]_D^{20}$ +12.76 (c 1.05, $CHCl_3$); mp: 51.5 °C.

5.1.7. (+)-(1*S*,5*S*,7a*S*)-5-(8′-Bromo-octyl)-1-methyl-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one (9). Alcohol **8** (4.64 g, 17.23 mmol, 1 equiv) and triphenylphosphine (5.9 g, 22.4 mmol, 1.3 equiv) were dissolved in dry THF (86 mL). Then carbon tetrabromide (7.43g, 22.4 mmol, 1.3 equiv) in acetonitrile (28 mL) was added at 0 °C in 30 min under magnetic stirring. Afterwards the reaction mixture was stirred at room temperature for further 3 h. The solvent was removed at reduced pressure and the yellow residue was purified by column chromatography on silica gel (∅ 6 cm×10.5 cm, EtOAc/*n*-hexane 1:7) to yield 5.6 g (16.8 mmol, 98%) of bromide **9** as light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.24–1.36 (br m, 8H, H_2C-2′–H_2C-5′), 1.37–1.47* (m, 3H, H_bC-1′ and H_2C-6′), 1.43* (d, J=6.1 Hz, 3H, H_3C–C-1), 1.58 (m, 1H, H_βC-7), 1.85* (quin, J=7.2 Hz, 2H, H_2C-7′), 1.93* (m, 2H, H_βC-6 and H_αC-7), 2.16 (m, 1H, H_αC-6), 2.27 (m, 1H, H_aC-1′), 3.41 (t, J=6.8 Hz, 2H, H_2C-8′), 3.51 (dddd, J_1=J_2=3.7 Hz, J_3=7.7 Hz, J_4=9.1 Hz, 1H, HC-5), 3.72 (ddd, J_1=9 Hz, J_2=8.2 Hz, J_3=6 Hz, 1H, HC-7a), 4.30 (dq, J_1=8 Hz, J_2=6.2 Hz, 1H, HC-1).

^{13}C NMR (100 Hz, $CDCl_3$): δ=19.62 (H_3C–C-1), 26.58 (H_2C-2′), 28.02 (H_2C-7), 28.08, 28.64, 29.30, 29.40 (4×CH_2, H_2C-3′–H_2C-6′), 30.50 (H_2C-1′), 32.76 (H_2C-8′), 33.45 (H_2C-6), 34.06 (H_2C-7′), 56.46 (HC-5), 67.80 (HC-7a), 78.75 (HC-1), 156.03 (OC-3).

IR (Golden Gate ATR) $\tilde{\nu}$=2926 (m), 2855 (m), 1743 (vs) [C═O], 1457 (m), 1406 (m), 1383 (m), 1360 (m), 1338 (m), 1308 (m), 1261 (m), 1222 (m), 1153 (w), 1045 (s), 919 (m), 799 (w), 764 (m), 723 (w), 680 (w), 643 (m), 610 (w) cm^{-1}.

EI-MS: m/z=334 ($[M+H]^+$, $[^{81}Br]$, 7.1%), 333 (M^+, $[^{81}Br]$, 13.4%), 332 ($[M+H]^+$, $[^{79}Br]$, 8.6%), 331 (M^+, $[^{79}Br]$, 12.5%), 69 (100%). HRMS (EI): calcd for $C_{15}H_{26}NO_2{}^{79}Br$: 331.114690; found: 331.114807. HRMS (ESI): calcd for $C_{15}H_{27}NO_2{}^{79}Br$ $[M+H]^+$: 332.1225; found: 332.1233.

$[\alpha]_D^{20}$ +16.46 (c 1.045, $CHCl_3$).

5.1.8. (+)-(1*S*,5*S*,7a*S*)-5-(8′-Iodo-octyl)-1-methyl-tetrahydro-pyrrolo[1,2-*c*]oxazol-3-one (10). To the solution of NaI (7.6 g, 50.4 mmol, 3 equiv) in acetone (17 mL) was added the solution of bromide **9** (5.6 g, 16.8 mmol, 1 equiv) in 17 mL of acetone. The mixture was stirred overnight (16 h) at room temperature. Precipitated NaBr was filtered off and the filtrate was concentrated by rotary evaporation. The pulpy yellow residue was purified by column chromatography to yield 6.33 g (16.7 mmol, 99.3%) of iodide **10** as an yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.21–1.35* (br, 8H, H_2C-2′–H_2C-5′), 1.38* (m, 2H, H_2C-6′), 1.44* (d, J=6.2 Hz,

3H, H_3C–C-1), 1.45* (m, 1H, H_bC-1′), 1.58 (m, 1H, $H_\beta C$-7), 1.81 (quin, J=7.1 Hz, 2H, H_2C-7′), 1.93 (m, 2H, $H_\beta C$-6 and $H_\alpha C$-7), 2.16 (m, 1H, $H_\alpha C$-6), 2.28 (m, 1H, H_aC-1′), 3.19 (t, J=7.0 Hz, 2H, H_2C-8′), 3.51 (dddd, J_1=J_2=3.7 Hz, J_3=7.7 Hz, J_4=9.1 Hz, 1H, HC-5), 3.73 (ddd, J_1=9.1 Hz, J_2=8.2 Hz, J_3=6 Hz, 1H, HC-7a), 4.30 (dq, J_1=8 Hz, J_2=6.2 Hz, 1H, HC-1).

^{13}C NMR (100 Hz, $CDCl_3$): δ=7.41 (H_2C-8′), 19.61 (H_3C–C-1), 26.55 (H_2C-2′), 28.00 (H_2C-7), 28.40, 29.27, 29.39, 30.39 (4×CH_2, H_2C-3′–H_2C-6′), 30.47 (H_2C-1′), 33.44, 33.46 (H_2C-6 and H_2C-7′), 56.41 (HC-5), 67.77 (HC-7a), 78.72 (HC-1), 156.00 (OC-3).

IR (Golden Gate ATR): $\tilde{\nu}$=2924 (m), 2853 (m), 1744 (vs) [C═O], 1458 (m), 1406 (m), 1383 (m), 1361 (m), 1260 (m), 1212 (m), 1044 (s), 916 (m), 764 (m), 722 (w), 681 (w), 649(w) cm^{-1}.

EI-MS: m/z=380 ([M+H]$^+$, 5.5%), 379 (M^+, 15.7%), 96 (100%). HRMS (EI): calcd for $C_{15}H_{26}NO_2I$: 379.100831; found: 379.100902. HRMS (ESI): calcd for $C_{15}H_{27}NO_2I$ [M+H]$^+$: 380.1087; found: 380.1102.

$[\alpha]_D^{20}$ +15.52 (c 0.525, $CHCl_3$).

5.1.9. (+)-(1′*S*,5′*S*,7a′*S*)-12-(1′-Methyl-3′-oxo-tetrahydro-pyrrolo[1,2-*c*]oxazol-5′-yl)-3-oxo-dodecanoic acid methyl ester (11). NaH (2.3 g, 60% in oil dispersion, 55.85 mmol, 1.25 equiv) was stirred in dry THF (100 mL) under an atmosphere of nitrogen and cooled to −5 °C. To this suspension a solution of methyl acetoacetate (5.19 g, 44.7 mmol, 1 equiv) in THF (10 mL) was added dropwise over 10 min below 0 °C. After additional stirring at −5 °C for 10 min, 35 mL of *n*-BuLi solution (15% solution in *n*-hexane, 55.85 mmol, 1.25 equiv) was added dropwise for 25 min below a temperature of +5 °C. The resulting yellow-orange mixture was stirred for an additional 5 min at −5 °C and then treated with a solution of iodide **10** (5.1 g, 13.4 mmol, 0.3 equiv) in THF (15 mL) for 5 min. The reaction mixture was allowed to warm slowly to 18 °C within 5 h before being quenched with ice water (70 mL) and 33 mL of 1 M citric acid adjusting to pH 6. Then the THF was removed by rotary evaporation and the aqueous residue was extracted with MTB ether (5×100 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (∅ 5 cm× 17 cm, EtOAc/*n*-hexane 1:9–1:3) afforded the β-oxoester **11** (3.18 g, 8.65 mmol, 64.5%) as an yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.19–1.36 (br, 12H, H_2C-6–H_2C-11), 1.42* (m, 1H, H_bC-12), 1.43* (d, J=6.5 Hz, 3H, H_3C–C-1′), 1.58 (m, 3H, H_2C-5 and $H_\beta C$-7′), 1.93 (m, 2H, $H_\beta C$-6′ and $H_\alpha C$-7′), 2.16 (m, 1H, $H_\alpha C$-6′), 2.27 (m, 1H, H_aC-12), 2.53 (t, J=7.3 Hz, 2H, H_2C-4), 3.46 (s, 2H, H_2C-2), 3.51 (dddd, J_1=J_2=3.7 Hz, J_3=7.6 Hz, J_4=9.3 Hz, 1H, HC-5′), 3.73* (m, 1H, HC-7a′), 3.74* (s, 3H, OCH_3), 4.30 (dq, J_1=8 Hz, J_2=6.3 Hz, 1H, HC-1′).

^{13}C NMR (100 Hz, $CDCl_3$): δ=19.62 (H_3C–C-1′), 23.43 (H_2C-5), 26.62 (H_2C-11), 28.02 (H_2C-7′), 28.94, 29.26, 29.30, 29.44, 29.49 (5×CH_2, H_2C-6–H_2C-10), 30.54 (H_2C-12), 33.46 (H_2C-6′), 43.08 (H_2C-4), 49.02 (H_2C-2), 52.32 (OCH_3), 56.47 (HC-5′), 67.84 (HC-7a′), 78.76 (HC-1′), 156.04 (OC-3′), 167.72 (OC-1), 202.91 (OC-3).

IR (Golden Gate ATR) $\tilde{\nu}$: 2925 (m), 2854 (m), 1742 (vs) [C═O], 1713 (s) [C═O], 1650 (w), 1437 (m), 1407 (m), 1384 (m), 1361 (m), 1319 (m), 1261 (m), 1221 (m), 1155 (m), 1050 (m), 905 (w), 801 (w), 766 (w), 722 (w), 681 (w), 651 (w) cm^{-1}.

EI-MS: m/z=368 ([M+H]$^+$, 6.4%), 367 (M^+, 8.8%), 252 (100%). HRMS (EI): calcd for $C_{20}H_{33}NO_5$: 367.235874; found: 367.235669. HRMS (ESI): calcd for $C_{20}H_{34}NO_5$ [M+H]$^+$: 368.2437; found: 368.2443; calcd for $C_{20}H_{33}NO_5Na$ [M+Na]$^+$: 390.2256; found: 390.2253.

$[\alpha]_D^{20}$ +14.4 (c 1.0, $CHCl_3$).

5.1.10. (+)-(1′*S*,3*R*,5′*S*,7a′*S*)-3-Hydroxy-12-(1′-methyl-3′-oxo-tetrahydro-pyrrolo[1,2-*c*]oxazol-5′-yl)-dodecanoic acid methyl ester 12. $[RuCl_2(p\text{-cymene})]_2$ (69.9 mg, 0.11 mmol) and (*R*)-(+)-BINAP (138.4 mg, 0.22 mmol) were placed under an atmosphere of nitrogen in the pressure flask of a hydrogenation apparatus and were dissolved in 5 mL of degassed DMF. After stirring at 110 °C for 20 min the DMF was removed in vacuo to yield a dark orange solid. Then the solution of the β-oxoester **11** (2.5 g, 6.9 mmol) in 30 mL of degassed methanol was added to the solid catalyst via flexible needle. The resulting mixture was treated with hydrogen (5 bar) at 70 °C under stirring for 24 h. After cooling to room temperature the dark orange solution was concentrated in vacuo and purified by flash chromatography (∅ 2.8 cm×10.7 cm, EtOAc/*n*-hexane, 1:9 to 1:3) to afford 2.3 g of β-hydroxyester **12** (6.22 mmol, 90.2%) as dark green solid (the product still contained small traces of the ruthenium complex, which could not be removed by column chromatography). Since the NMR spectra showed no trace of the (3*S*)-epimer the estimated was dr >99:1 in favour for the desired (3*R*)-epimer.

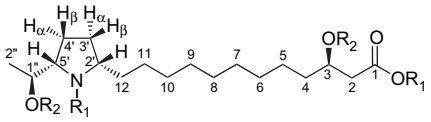
^{1}H NMR (400 MHz, $CDCl_3$): δ=1.20–1.36* (br, 13H, H_2C-5–H_2C-10 and H_bC-11), 1.36–1.64* (m, 5H, H_bC-12, H_aC-11, H_2C-4, $H_\beta C$-7′), 1.43* (d, J=6.1 Hz, 3H, H_3C–C-1′), 1.93 (m, 2H, $H_\beta C$-6′ and $H_\alpha C$-7′), 2.16 (m, 1H, $H_\alpha C$-6′), 2.27 (m, 1H, H_aC-12), 2.42 (dd, J_1=16.4 Hz, J_2=8.9 Hz, 1H, H_aC-2), 2.52 (dd, J_1=16.4 Hz, J_2=3.1 Hz, 1H, H_bC-2), 2.97 (d, J=3.7 Hz, 1H, OH), 3.51 (dddd, J_1=J_2=3.8 Hz, J_3=7.8 Hz, J_4=9.2 Hz, 1H, HC-5′), 3.71* (s, 3H, OCH_3), 3.72* (m, 1H, HC-7a′), 4.00 (apparent o, J=3.7 Hz, HC-3), 4.30 (dq, J_1=8.1 Hz, J_2=6.2 Hz, 1H, HC-1′).

^{13}C NMR (100 Hz, $CDCl_3$): δ=19.61 (H_3C–C-1′), 25.44 (H_2C-5), 26.62 (H_2C-11), 28.01 (H_2C-7′), 29.43, 29.45, 29.47, 29.49, 29.51 (5×CH_2, H_2C-6–H_2C-10), 30.54 (H_2C-12), 33.46 (H_2C-6′), 36.55 (H_2C-4), 41.18 (H_2C-2), 51.71 (OCH_3), 56.47 (HC-5′), 67.83 (HC-7a′), 68.00 (HC-3), 78.77 (HC-1′), 156.05 (OC-3′), 173.47 (OC-1).

IR (Golden Gate ATR) $\tilde{\nu}$=3517 (m) [O–H], 2924 (m), 2854 (m), 1733 (vs) [C═O], 1469 (m), 1446 (m), 1402 (m), 1390 (m), 1367 (s), 1339 (m), 1323 (m), 1304 (m), 1259 (s), 1221 (m), 1202 (m), 1170 (s), 1151 (s), 1128 (m), 1095 (m), 1056 (s), 1030 (s), 996 (m), 924 (w), 909 (w), 864 (m), 802 (w), 768 (m), 721 (w), 680 (w), 650 (w) cm^{-1}.

EI-MS: m/z=370 ([M+H]$^+$, 11.8%), 369 (M$^+$, 8.0%), 69 (100%). HRMS (EI): calcd for $C_{20}H_{35}NO_5$: 369.251524; found: 369.251298. HRMS (ESI): calcd for $C_{20}H_{36}NO_5$ [M+H]$^+$: 370.2593; found: 370.2592.

$[\alpha]_D^{20}$ +5.81 (c 1.1, $CHCl_3$); mp: 30 °C.



1: $R_1 = R_2 = H$
13: $R_1 = CH_3$, $R_2 = H$
14: $R_1 = CH_3$, R_2 = MTPA

5.1.11. (+)-(1″*S*,2′*S*,3*R*,5′*S*)-3-Hydroxy-12-[5-(1″-hydroxy-ethyl)-pyrrolidin-2′-yl]-dodecanoic acid—betain form ((+)-morusimic acid B) (1). A suspension of $Ba(OH)_2 \cdot 8H_2O$ (1.9 g, 6 mmol, 6 equiv) in H_2O (30 mL) was added in one portion to the solution of (3*S*)-hydroxyester **12** (370 mg, 1 mmol, 1 equiv) in 1,4-dioxane (45 mL). This mixture was refluxed for 24 h at 110 °C. After cooling to room temperature most of the solvent mixture was evaporated leaving ca. 15 mL of an aqueous alkaline residue. This was thinned with distd water (30 mL) and adjusted to pH 6 with 2 N sulfuric acid under continuous pH control (pH metre). The precipitated barium sulfate was filtered off through a glass frit and was washed with MeOH (3× 30 mL). The solution was concentrated in vacuo to afford 400 mg of the crude amino acid as a white solid still containing a small amount of $BaSO_4$. Recrystallization from MeOH provided 300 mg (0.91 mmol, 91%) of spectroscopically pure (+)-morusimic acid B betain as a white powder.

^{1}H NMR (400 MHz, CD_3OD): see Table 2.

^{13}C NMR (100 Hz, CD_3OD): see Table 2.

IR (Golden Gate ATR) *Pyrrolidinium trifluoroacetate*: $\tilde{\nu}$=3275 (b) [O–H], 2918 (vs), 2849 (s), 1677 (vs), 1628 (m), 1556 (s), 1538 (s), 1465 (m) 1406 (vs), 1386 (s), 1299 (m), 1257 (m), 1204 (vs), 1180 (vs), 1132 (vs), 1102 (m), 1045 (m), 986 (w), 971 (w), 926 (w), 904 (w), 872 (w), 842 (m), 802 (m), 758 (vw), 722 (s), 651 (w), 625 (w) cm^{-1}.

IR (Golden Gate ATR) *Betain (pH 6–7)*: $\tilde{\nu}$ 3271 (b) [O–H], 2916 (s), 2849 (s), 2480 (b) [N–H], 1628 (m), 1532 (s) [C=O], 1464 (m), 1441 (s), 1406 (vs), 1386 (s), 1340 (m), 1303 (m), 1251 (m), 1177 (m), 1155 (m), 1101 (m), 1084 (m), 1045 (s), 969 (m), 929 (m), 905 (m), 873 (m), 762 (w), 720 (m), 651 (w), 626 (w) cm^{-1}.

EI-MS: m/z=330 ([M+H]$^+$, 2.1%), 284 (100%). HRMS (EI): calcd for $C_{18}H_{36}NO_4$: 330.264434; found: 330.264435. HRMS (ESI): calcd for $C_{18}H_{36}NO_4$: 330.2644; found: 330.2644.

$[\alpha]_D^{20}$ (betain) +8.33 (c 0.42, MeOH); mp (betain): 172±2 °C (decomposition).

5.1.12. (+)-(1″*S*,2′*S*,3*R*,5′*S*)-3-Hydroxy-12-[5-(1″-hydroxy-ethyl)-1′-methyl-pyrrolidin-2′-yl]-dodecanoic acid methyl ester ((+)-*N*-methyl morusimic acid B methyl ester) (13). The solution of (+)-morusimic acid B **1** (165 mg, 0.5 mmol) in MeOH (40 mL) was treated with a solution of diazomethane in ether (prepared from *p*-toluenesulfonyl-*N*-methyl-*N*-nitrosamide (21.5 g) in Et_2O with KOH (5 g) in H_2O (8 mL) and EtOH (25 mL) at 80 °C) in excess at 0 °C. After stirring overnight at room temperature the solvent was removed under reduced pressure and the yellow sticky residue was subjected to flash chromatography (∅ 1.6 cm×10 cm, MTB ether/MeOH 10:1) to yield 125 mg of *N*-methyl morusimic acid B methyl ester **13** (0.35 mmol, 70%) as an yellow-orange oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.13 (d, J=6.1 Hz, 3H, H_3C-2″), 1.28* (br, 14H, H_aC-5, H_2C-6–H_2C-11 and H_bC-12), 1.33–1.57* (m, 5H, $H_\alpha C$-3′, $H_\alpha C$-4′, H_2C-4 and H_bC-5), 1.62 (m, 1H, H_bC-12), 1.85 (m, 2H, $H_\beta C$-3′ and $H_\beta C$-4′), 2.41* (dd, J_1=16.5 Hz, J_2=9.2 Hz, 1H, H_aC-2), 2.42* (m, 2H, HC-2′ and HC-5′), 2.45* (s, 3H, NCH_3), 2.51 (dd, J_1=16.0 Hz, J_2=3.4 Hz, 1H, H_bC-2), 3.32 (quin, J=6.4 Hz, 1H, HC-1″), 3.71 (s, 3H, OCH_3), 4.00 (m, 1H, HC-3).

^{13}C NMR (100 Hz, $CDCl_3$): δ=20.71 (H_3C-2″), 25.48, 26.56 (H_2C-5 and H_2C-11), 27.42 (H_2C-4′), 29.49, 29.50, 29.53, 29.60, 29.97 (5×CH_2, H_2C-6–H_2C-10), 31.11 (H_2C-3′), 35.10 (H_2C-12), 36.61 (H_2C-4), 41.24 (H_2C-2), 43.84 (NCH_3), 51.70 (OCH_3), 67.99 (HC-3), 68.80 (HC-2′), 70.23 (HC-1″), 72.56 (HC-5′), 173.44 (OC-1).

IR (Golden Gate ATR) $\tilde{\nu}$=3414 (b) [O–H], 2924 (vs), 2853 (s), 2787 (m), 1737 (s) [C=O], 1459 (m), 1438 (s), 1369 (m), 1290 (m), 1198 (s), 1168 (s), 1120 (s), 1044 (s), 901 (m), 723 (w), 646 (w), 611 (w) cm^{-1}.

EI-MS: m/z=357 (M$^+$, 2.1%), 312 (100%). HRMS (EI): calcd for $C_{20}H_{39}NO_4$: 357.287909; found: 357.287787. HRMS (ESI): calcd for $C_{20}H_{40}NO_4$ [M+H]$^+$: 358.2957; found: 358.2056.

$[\alpha]_D^{20}$ +32.72 (c 1.03, $CHCl_3$).

5.1.13. (*R*)-(+)-MTPA ester (14a) and (*S*)-MTPA ester (14b). *N*-Methyl morusimic acid B methyl ester **13** (14.3 mg, 40 μmol, 1 equiv) and DMAP (1 mg) were dissolved in dry DCM (2 mL) and treated consecutively with NEt_3 (24 mg, 23.7 μmol, 5.9 equiv) and (26 mg, 48 μmol, 2.4 equiv) *S*-(+)-MTPA chloride. After stirring at room temperature for 1 h the reaction mixture was quenched with 2 mL of phosphate buffer, pH 7. The aqueous phase was extracted with DCM (2×3 mL). The combined organic extracts were dried over Na_2SO_4, concentrated in vacuo and the yellow sticky residue was chromatographed (∅ 1.6 cm×11 cm, EtOAc/*n*-hexane, 1:10–1:7) affording 24.4 mg (32.2 μmol, 80.4%) of (*R*)-MTPA ester **14a**. The same procedure was carried out with (*R*)-(−)-MTPA chloride yielding 23 mg (29.1 μmol, 72.8%) of (*S*)-MTPA ester **14b**.

5.1.13.1. (*R*)-(+)-MTPA ester (14a). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.072–1.333* (br m, 16H, H_2C-5–H_2C-12), 1.276* (d, J=6.5 Hz, 3H, H_3C-2″), 1.477–1.715 (m, 5H, H_2C-3′, H_2C-4′, HC-4), 1.765 (m, 1H, HC-4), 2.191* (s, 3H, NCH_3), 2.243* (m, 1H, HC-2′), 2.604* (dd,

J_1=16 Hz, J_2=4.8 Hz, 1H, H_aC-2), 2.615* (m, 1H, HC-5′), 2.697 (dd, J_1=16 Hz, J_2=8 Hz, H_bC-2), 3.543 (q, J=1.2 Hz, 3H, OCH_3), 3.569 (q, J=1.2 Hz, 3H, OCH_3), 3.660 (s, 3H, $COOCH_3$), 5.161 (quin, J=6.1 Hz, 1H, HC-1″), 5.475 (m, 1H, HC-3), 7.350–7.420 (m, 6H, MTPA–ArH), 7.500–7.580 (m, 4H, MTPA–ArH).

^{13}C NMR (100 Hz, $CDCl_3$): δ=14.49 (H_3C-2″), 24.04, 24.62, 26.17, 29.17, 29.36, 29.43, 29.61, 30.06, 30.29 (9×CH_2, H_2C-3′, H_2C-4′ and H_2C-2–H_2C-11), 33.61 (H_2C-12), 34.22 (H_2C-4), 38.59 (H_2C-2), 40.44 (NCH_3), 51.89 (OCH_3), 55.39 (q, J=1.4 Hz, MTPA–OCH_3), 55.44 (q, J=1.6 Hz, MTPA–OCH_3), 67.66 (HC-2′), 67.94 (HC-5′), 73.32 (HC-3), 75.31 (HC-1″), 121.92 (d, J=11.1 Hz, MTPA–CF_3), 124.78 (d, J=11.1 Hz, MTPA–CF_3), 127.32, 127.33, 127.35, 127.36, 128.27, 128.32, 129.43, 129.55 (10×CH, MTPA–ArCH), 132.31, 132.55 (2×C_q, MTPA–ArC_q), 165.94, 165.97 (2×CO, MTPA–CO), 170.53 (OC-1).

HRMS (ESI): calcd for $C_{40}H_{53}NO_8F_6$ $[M+H]^+$: 790.3754; found: 790.3774.

$[\alpha]_D^{20}$ +42.2 (c 1.27, $CHCl_3$).

5.1.13.2. (*S*)-(−)-MTPA ester (14b). ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.133–1.376 (br m, 16H, H_2C-5–H_2C-12), 1.217 (d, J=6.5 Hz, 3H, H_3C-2″), 1.574–1.772 (m, 5H, H_2C-3′, H_2C-4′ and HC-4), 2.291* (s, 3H, NCH_3), 2.302* (m, 1H, HC-2′), 2.572 (dd, J_1=15.9 Hz, J_2=5 Hz, 1H, H_aC-2), 2.647* (dd, J_1=15.9 Hz, J_2=8 Hz, 1H, H_bC-2), 2.669* (m, 1H, HC-5′), 3.528 (d, J=1.0 Hz, 3H, OCH_3), 3.542 (d, J=1.0 Hz, 3H, OCH_3), 3.586 (s, 3H, $COOCH_3$), 5.095 (quin, J=6.1 Hz, 1H, HC-1″), 5.477 (m, 1H, HC-3), 7.350–7.420 (m, 6H, MTPA–ArH), 7.500–7.610 (m, 4H, MTPA–ArH).

^{13}C NMR (100 Hz, $CDCl_3$): δ=14.62 (H_3C-2″), 24.51, 25.00, 26.25, 29.23, 29.40, 29.45, 29.62, 30.07, 30.45 (9×CH_2, H_2C-3′, H_2C-4′ and H_2C-2–H_2C-11), 33.77 (H_2C-12), 34.50 (H_2C-4), 38.44 (H_2C-2), 40.90 (NCH_3), 51.80 (OCH_3), 55.27 (q, J=1.5 Hz, MTPA–OCH_3), 55.37 (q, J=1.5 Hz, MTPA–OCH_3), 67.84 (HC-2′), 68.25 (HC-5′), 73.50 (HC-3), 75.93 (HC-1″), 121.93 (d, J=11.1 Hz, MTPA–CF_3), 124.80 (d, J=11.1 Hz, MTPA–CF_3), 127.46, 127.47, 127.60, 127.61, 128.31, 128.35, 129.49, 129.54 (10×CH, MTPA–ArCH), 132.18, 132.46 (2×C_q, MTPA–ArC_q), 165.87, 166.21 (2×CO, MTPA–CO), 170.32 (OC-1).

HRMS (ESI): calcd for $C_{40}H_{53}NO_8F_6$ $[M+H]^+$: 790.3754; found: 790.3751.

$[\alpha]_D^{20}$ −17.45 (c 1.41, $CHCl_3$).

5.1.14. (±)-11-Benzyloxy-undec-1-en-3-ol (16). (1) *Monoprotection*. Nonane-1,9-diol (8 g, 50 mmol, 1 equiv) was dissolved in dry DCM (150 mL) under slight warming (40–50 °C). To the clear solution freshly prepared silver(I) oxide[17] (17.4 g, 75 mmol, 1.5 equiv) was added under vigorous stirring with a *KPG* stirrer. Then the dark brown suspension was slowly treated with benzyl bromide (9.4 g, 55 mmol, 1.1 equiv). After stirring overnight at room temperature the Ag_2O was filtered off through a silica gel pad and washed with DCM (3×50 mL). The solvent was removed in vacuo to leave 11.7 g of an yellow oil as crude product. Purification by column chromatography (∅ 4.6 cm×11 cm, EtOAc/*n*-hexane 1:8, then pure EtOAc) gave 8.3 g (33.2 mmol) of the monoprotected diol (66% yield) as well as 2.66 g (7.8 mmol, 15.6%) of the dibenzylated diol and 1.1 g (6.9 mmol, 13.8%) of the unprotected diol.

(2) *Swern oxidation*. To a solution of oxalyl chloride (4.6 g, 36.3 mmol, 1.1 equiv) in dry DCM (74 mL) was added slowly dry DMSO (5.67 g, 72.6 mmol, 2.2 equiv) at −65 °C under an atmosphere of nitrogen. After recooling to −78 °C a solution of the monoprotected diol (8.26 g, 33 mmol, 1 equiv) in dry DCM (17 mL) was added dropwise under vigorous stirring. After 30 min the reaction mixture was slowly treated with dry NEt_3 (16.7 g, 165 mmol, 5 equiv) the temperature being kept below −60 °C. Then the reaction mixture was allowed to warm slowly to 0 °C and was stirred at this temperature for additional 60 min. The reaction mixture was quenched with ice water (50 mL) and the aqueous phase was extracted with DCM (2×50 mL). The combined organic phases were washed with an equal volume of 1 M hydrochloric acid and 5% $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated under reduced pressure to afford 7.9 g (96%) of the aldehyde that was used for the next step without further purification.

(3) *Grignard addition*. A solution of vinylmagnesium chloride (25 mL, 42.5 mmol, 1.4 equiv, 1.7 M in THF) was cooled to −30 °C under an atmosphere of nitrogen and treated with the crude aldehyde (7.7 g, 31 mmol, 1 equiv) in dry THF (10 mL) at −10 °C to −5 °C. The reaction mixture was allowed to warm to room temperature and was stirred at this temperature for an additional 2 h. Then the mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with Et_2O (3×100 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo to afford 8.53 g of the crude product, which was purified by column chromatography (∅ 4 cm×11 cm, EtOAc/*n*-hexane 1:10→1:6) yielding 7.15 g (25.9 mmol) of the allylic alcohol **16** (51.8% over three steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22–1.43 (br m, 10H, H_2C-5–H_2C-9), 1.51 (m, 2H, H_2C-4), 1.61 (apparent quin, J=7 Hz, 2H, H_2C-10), 1.74 (d, J=3.9 Hz, 1H, OH), 3.46 (t, J=6.6 Hz, 2H, H_2C-11), 4.08 (qt, J_1=6.4 Hz, J_2=1.2 Hz, 1H, HC-3), 4.50 (s, 2H, $OCH_2C_6H_5$), 5.09 (dt, J_1=10.4 Hz, J_2=1.3 Hz, 1H, HC-1), 5.21 (dt, J_1=17.2 Hz, J_2=1.4 Hz, 1H, HC-1), 5.86 (ddd, J_1=17.1 Hz, J_2=10.5 Hz, J_3=6.3 Hz, 1H, HC-2), 7.23–7.37 (m, 5H, Ar–CH).

^{13}C NMR (100 Hz, $CDCl_3$): δ=25.30, 26.15, 29.38, 29.47, 29.50, 29.72 (6×CH_2, H_2C-5–H_2C-10), 37.01 (H_2C-4), 70.46 (H_2C-11), 72.82 ($OCH_2C_6H_5$), 73.19 (HC-3), 114.47 (H_2C-1), 126.31, 127.45, 127.61, 128.32, 128.50 (5×CH, Ar–CH), 138.65 (Ar–C_q), 141.35 (HC-2).

IR (Golden Gate ATR) $\tilde{\nu}$=3413 (b) [O–H], 3065 (m), 3030 (m), 2929 (vs), 2855 (vs), 1951 (w), 1809 (w), 1710 (m), 1644 (m), 1455 (s), 1362 (s), 1309 (m), 1206 (m), 1098 (vs), 1028 (s), 991 (s), 919 (s), 735 (s), 697 (s), 613 (w) cm^{-1}.

EI-MS: m/z=276 (M^+, 1.1%), 107 (100%). HRMS (EI): calcd for $C_{18}H_{28}O_2$: 276.208930; found: 276.208099.

5.1.15. (2*E*)-11-Benzyloxy-1-bromo-undec-2-en (17a). Under an atmosphere of nitrogen a solution of allylic alcohol **16** (7 g, 25.3 mmol, 1 equiv) in dry petrol ether (7 mL) was added dropwise to PBr_3 (0.95 mL, 2.74 g, 10.1 mmol, 0.4 equiv) and dry pyridine (0.3 g, 3.8 mmol, 0.15 equiv) in PE (5 mL) keeping the temperature below −5 °C. The resulting mixture was stirred at room temperature for an additional 80 min, subsequently quenched with ice water (20 mL) and the aqueous phase extracted with petrol ether (3×25 mL). The combined organic phases were washed carefully with small amounts of saturated $NaHCO_3$ solution to neutralize HBr, dried over Na_2SO_4 and evaporated under reduced pressure. The remaining yellow oil was chromatographed (∅ 4 cm×10 cm, EtOAc/*n*-hexane, 1:100→1:75→1:50→1:25) to give a 2:1 mixture of allylic bromides **17a** and **17b** (84% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ=1.18–1.48 (br m, 10H, H_2C-5–H_2C-9), 1.61 (apparent quin, J=7 Hz, 2H, H_2C-10), 2.04 (apparent q, J=6.9 Hz, 2H, H_2C-4), 3.46 (t, J=6.6 Hz, 2H, H_2C-11), 3.93 (d, J=7.5 Hz, 2H, H_2C-1), 4.49 (s, 2H, O$CH_2C_6H_5$), 5.67 (dt, J_1=15.0 Hz, J_2=7.4 Hz, 1H, HC-2), 5.76 (dt, J_1=15.0 Hz, J_2=6.3 Hz, 1H, HC-3), 7.23–7.36 (m, 5H, Ar–CH).

^{13}C NMR (100 Hz, $CDCl_3$): δ=26.15, 28.75, 29.00, 29.34, 29.36, 29.74, 32.03 (7×CH_2, H_2C-4–H_2C-10), 33.62 (H_2C-1), 70.46 (H_2C-11), 72.84 (O$CH_2C_6H_5$), 126.25 (HC-2), 127.43, 127.58, 128.31 (5×CH, Ar–CH), 136.69 (HC-3), 138.70 (Ar–C_q).

IR (Golden Gate ATR) $\tilde{\nu}$=3030 (w), 2926 (s), 2853 (s), 1660 (w), 1496 (w), 1454 (m), 1362 (m), 1308 (w), 1203 (s), 1099 (vs), 1028 (m), 964 (s), 733 (vs), 697 (vs) cm^{-1}.

EI-MS: m/z=340 ([M+H]$^+$, [^{81}Br], 26.0%), 339 (M^+, [^{81}Br], 51.5%), 338 ([M+H]$^+$, [^{79}Br], 23.9%), 337 (M^+, [^{79}Br], 49.25%), 107 (100%). HRMS (EI): calcd for $C_{15}H_{26}NO_2{}^{79}$Br: 338.124527; found: 338.124725.

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