Graphical Abstract:

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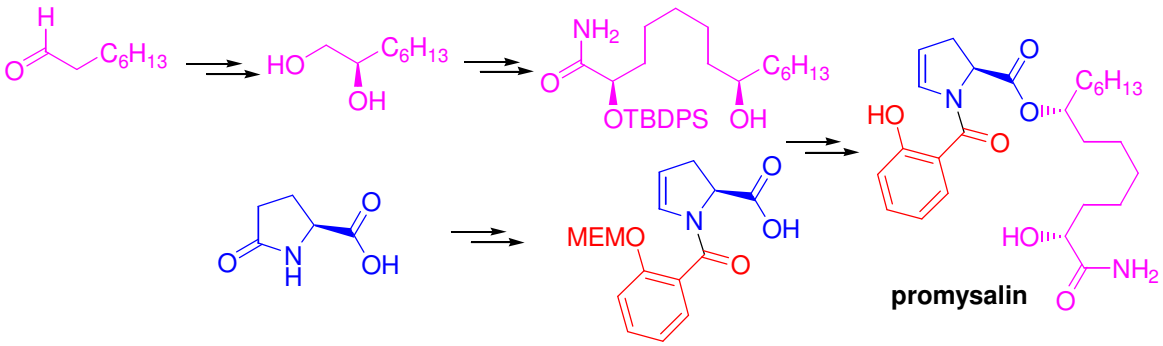

Total synthesis of the salicyldehydroproline-containing antibiotic Promysalin

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Abstract: A convergent total synthesis of Promysalin, a metabolite of *Pseudomonas putida* RW10S1 with antibiotic activity, is described. The synthetic approach is based around a salicyldehydroproline core and a dihydroxymyristamide fragment. Crucial steps include a MacMillan asymmetric α-hydroxylation applied for the construction of the myristamide framework, and a lactam reduction by Superhydride ® to obtain the dehydroproline fragment. Because of the modular nature of the synthesis, ready access to analogues for biological evaluation is available.

***Keywords*:** natural products, total synthesis, stereoselectivity, antibiotics

1. Introduction

To survive in a world with limited resources microorganisms have developed elaborate mechanisms such as the formation of biofilms and the production of antimicrobial toxins. A plethora of new antimicrobial agents have been discovered *via* the elucidation of the chemical compounds used in this bacterial warfare. Indeed, natural products directly from bacterial sources account for the majority of currently employed antibiotics.[1] Despite having complex structure, these compounds are sources of chemical diversity and leads arising from them are often more bio-friendly, due to their co-evolution with the target sites in biological systems.

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In 2011, Li et al.[2] isolated a novel metabolite, promysalin (**1**, Figure 1) produced by a rice-associated *Pseudomonas* strain *(Pseudomonas putida*, RW10S1).

Promysalin displayed a remarkable antagonistic spectrum, selectively inhibiting the growth of other *Pseudomonas*, including *P. aeruginosa*, at low micromolar concentrations. The compound was also shown to promote swarming of the producing organism and surface colonization. The most recent studies[3] have demonstrated that promysalin disperses established biofilms and inhibits pyoverdine production, two pathogenic phenotypes, which may hint at the role the metabolite plays in the rhizosphere. These results increased the interest for the compound.
Li. et al.[2] elucidated the structure of promysalin by spectroscopic methods. The compound is composed of salicylic acid and 2,8-dihydroxymyristamide connected by a 2-pyrroline-5-carboxy moiety. However, no relative or absolute stereochemical assignments at C2, C8 and C16 were made in the original paper.

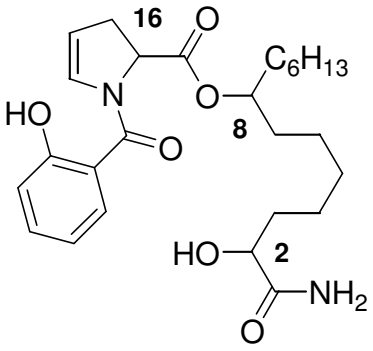
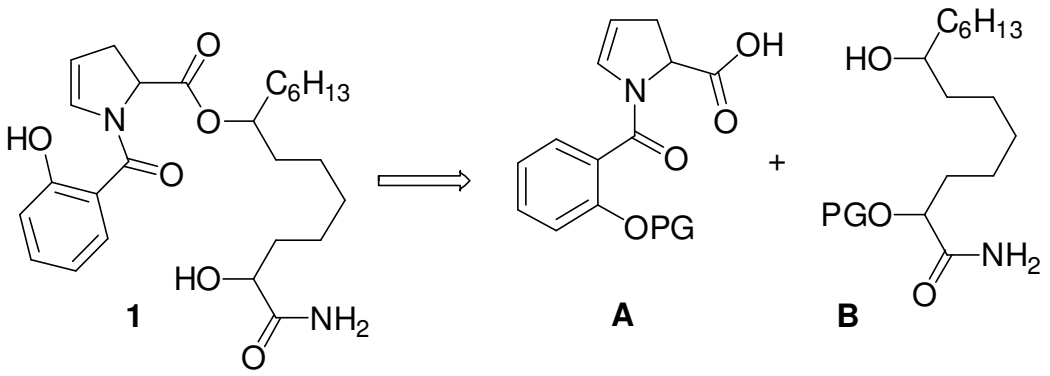


Fig. 1. Structure of promysalin (**1**).

2. Result and Discussion

Due to its intriguing structure and unique bioactivity, we planned to develop a stereoselective synthesis of **1**, which may, in principle, have a value in the preparation of promysalin itself as well as various analogues.

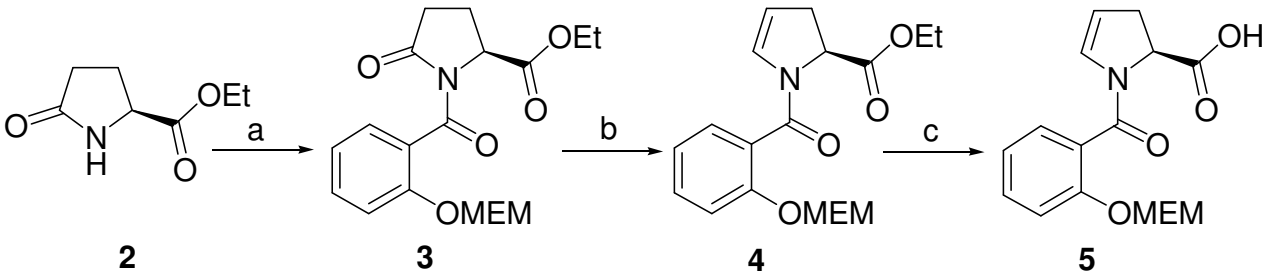
The molecule, which can be retrosynthetically disconnected at the ester bond, appears well suited to a convergent synthetic approach based around a salicyldehydroproline core (**A**) and a dihydroxymyristamide fragment (**B**) (Scheme 1).



Scheme 1. Retrosynthetic analysis of promysalin. PG = Protecting Group.

We envisaged that the most straightforward approach for preparation of the dehydroproline moiety of fragment (**A**) could be a lactam reduction by Superhydride ® (lithium triethylborohydride solution), followed by *in situ* dehydration of the resulting lactamol with TFAA and DIPEA, according to Yu's procedure.[4]

As the absolute configuration at the three stereogenic centers had not been established in the original paper, we initially focused on the synthesis of a diastereoisomer arbitrarily chosen with the (*S*)-configuration at C16, by assuming the natural (*S*)-configuration of the proline core in the biosynthetic pathway.[1] Thus, (*S*)-pyroglutamic acid ethyl ester **2** was used as a chiral synthon for construction of the dehydroproline core (Scheme 2).



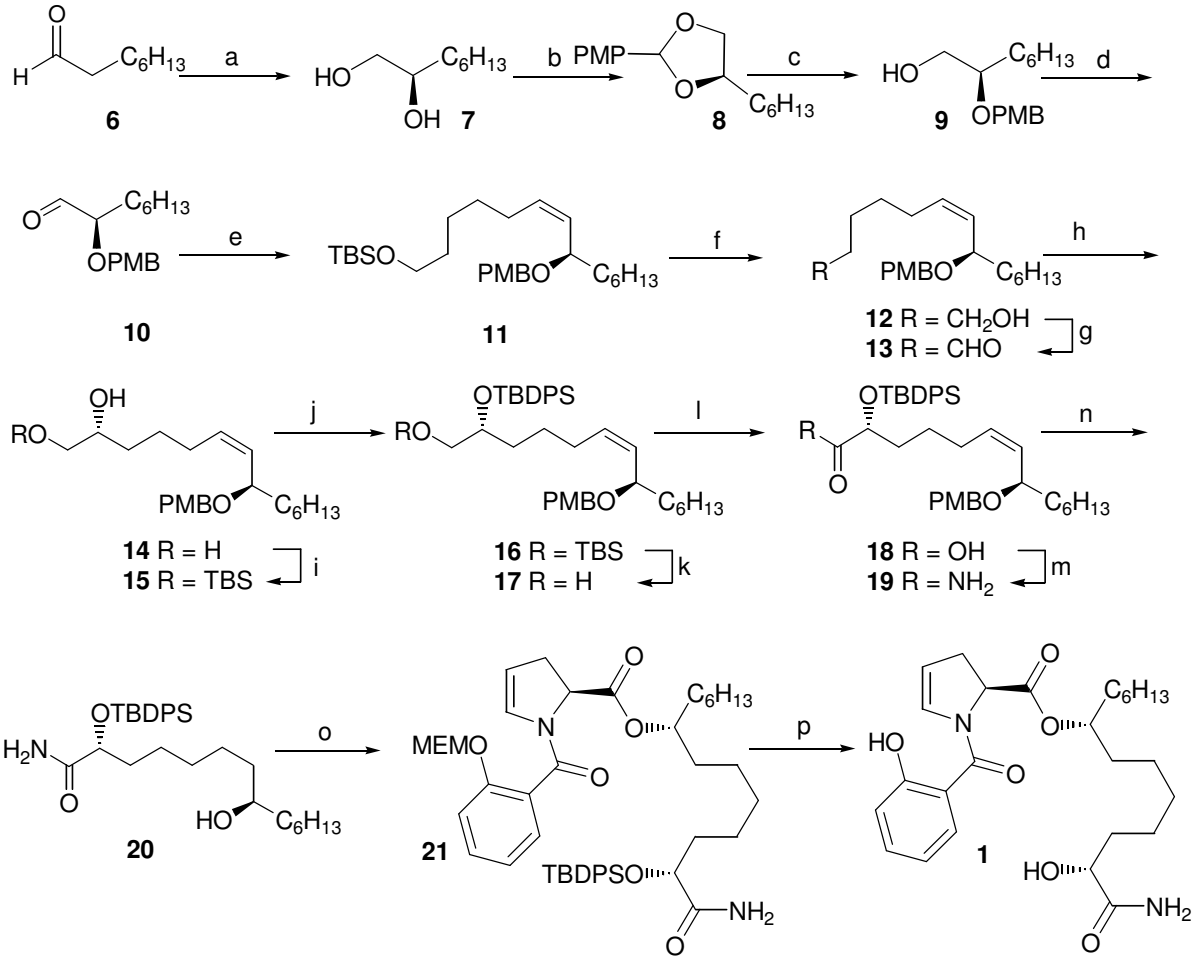
Scheme 2. Synthesis of the salicyldehydroproline core. Reagents and conditions: (a) i. 2-[(2-methoxyethoxy)methoxy]benzoic acid, 1-chloro-*N*,*N*,2-trimethyl-1-propenylamine, CH_2Cl_2, 0 °C to rt, 1 h; ii. NEt_3, toluene, 80 °C, 3 h, 82%; (b) $LiBHEt_3$, toluene, -78 °C, 1 h, then TFAA, DIPEA, cat. DMAP, -78 °C to rt, 3 h, 62%; (c) LiOH, EtOH : H_2O, 0 °C to rt, 5 h, 97%.

We planned to acylate the lactam with a suitably protected salicylic acid before the reduction. The choice of the phenolic protecting group proved to be nontrivial, as it affected the outcome of

the reductive elimination step. In fact, every attempt to use *O*-acetyl salicyloyl chloride (commercially available) led to the dehydroproline moiety in very poor yield, together with compounds deriving from hydrolysis of the acetate group. Replacement of acetate with allyl, benzyl, or 4-methoxybenzyl ethers led to the decomposition of the starting material. The use of 2-methoxyethoxymethyl (MEM) ether seemed to be more promising, as the MEM protected salicyl-5-oxopyrrolidine underwent smooth reduction to the lactamol, followed by base mediated *in situ* elimination to the dehydroproline, in good yield.

Having found a suitable protecting group, we proceeded with the synthesis of fragment **5**, (Scheme 2). Ethyl (*S*)-pyroglutamate **2** was acylated with 2-((2-methoxyethoxy) methoxy)benzoic acid[5] using Ghosez's reagent (1-chloro-*N*,*N*,2-trimethyl-1-propenylamine) and TEA in toluene[6] to obtain **3** in 82% yield. Lactam reduction of **3** using $LiBHEt_3$ at -78 °C, followed by treatment with TFAA and DIPEA[4] afforded compound **4** in 62% yield. Finally, basic hydrolysis of the ester gave key intermediate **5**.

With the salicyldehydroproline fragment in hand, attention was focused on the myristamide framework (**B**). We conceived that both hydroxy groups at C2 and C8 could be introduced in a stereoselective way using successive the proline-catalysed MacMillan asymmetric α-hydroxylations of carbonyl compounds[7] as key reactions. As the absolute configuration at C2 and C8 was unknown, this method could have the further advantage of providing access to all stereoisomers, by using the appropriate proline as a catalyst.



Scheme 3. Synthesis of dihydroxymyristamide fragment (B). Reagents and conditions: (a) i. L-proline, PhNO, $CHCl_3$, +4 °C, 2 h, then $NaBH_4$, EtOH, 0 °C, 0.5 h; ii. Zn dust, EtOH /AcOH, rt, 1 h, 91% over two steps; (b) PMB dimethylacetal, PPTS, CH_2Cl_2, 0 °C to rt, 2 h; (c) DIBAL, CH_2Cl_2, -78 °C, 2 h, 72% over two steps; (d) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C, 94%, 2 h; (e) *n*-BuLi, $TBSO(CH_2)_6P^+Ph_3Br^-$, THF, -78 °C to rt, 2 h, 74%; (f) TBAF, THF, 0 °C to rt, 1 h, 88%; (g) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78 °C, 1 h, 91%; (h) i. L-proline, PhNO, $CHCl_3$, + 4 °C, 2 h, then $NaBH_4$, EtOH, 0 °C, 0.5 h; ii. Zn dust, EtOH /AcOH, rt, 1 h, 77% over two steps; (i) TBS-Cl, imidazole, CH_2Cl_2, rt, 6 h, 98%; (j) TBDPS-Cl, imidazole, DMF, rt, 16 h, 98%; (k) AcOH /THF /H_2O, rt, 36 h, 92%; (l) TEMPO, bis(acetoxy)iodobenzene, $NaHCO_3$, MeCN : H_2O, 0 °C, 4 h, 70%; (m) HBTU, HOBT, NH_4Cl, DIPEA, DMF, 0 °C to rt, 1 h, 73%; (n) H_2, Pd/C, MeOH, rt, 12 h, 73%; (o) **5**, EDC, CH_2Cl_2, rt, 16 h, 50%; (p) i. $TiCl_4$, -20 °C, 15 min, ii. TBAF, THF, 0 °C to rt, 2 h, 70% over two steps.

Thus, commercially available octanal **6** was subjected to α-hydroxylation using L-proline and nitrosobenzene in $CHCl_3$ at +4 °C, followed by *in situ* reduction with $NaBH_4$ and treatment with

zinc to obtain diol **7**. The absolute configuration at C2 was assumed to be (*R*), following that in all the examples reported in literature[8] the aminoxylation reaction took place in the same stereochemical fashion. The optical rotation ($[\alpha]_D^{23}$ = +14.1 (c 1.00, MeOH); lit.[9] for (*S*)-1,2 octanediol ($[\alpha]_D^{23}$ = -13.6 (*c* 1.00, MeOH, e.e. 97%), confirmed that we had obtained the (*R*) enantiomer with more than 97% e.e.

Reaction with 4-methoxybenzaldehyde dimethylacetal in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) gave compound **8**, whose reductive cleavage with DIBAL provided protected alcohol **9**.[10]

Swern oxidation[11] of the primary alcohol gave aldehyde **10** in 94% yield. Elongation of the chain was readily effected by Wittig olefination with *tert*-butyldimethylsilyloxybutyl (triphenyl) phosphonium bromide.[12] Selective deprotection of the O-TBS group by TBAF at 0 °C[13] furnished the free primary alcohol **12**. The stereoselectivity of the reactions was assessed by catalytic hydrogenation of **12**, to obtain (*R*)-tetradecane-1,8-diol, whose optical purity and absolute configuration were confirmed by optical rotation measurement ($[\alpha]_D^{23}$ = -0.63 (*c* 1.1, $CHCl_3$; lit.[14] for (*R*) enantiomer $[\alpha]_D^{23}$ = -0.48 (*c* 1.1, $CHCl_3$, obtained by opening of an epoxide with 91% e.e.[15]); lit.[16] $[\alpha]_D^{23}$ = -0.6 (*c* 1.8, $CHCl_3$). Again, Swern oxidation followed by another α -oxyamination reaction allowed the stereoselective introduction of the hydroxy group at C2 in compound **14**. The (*R*) configuration at this carbon could be safely assumed on the basis of the mechanism of the reaction.[7]

The direct oxidation of 1,2 diol **14** to the corresponding α-hydroxycarboxylic acid gave complex mixtures.[17] After various unsuccessful attempts, the sequential protection of primary and secondary alcohol with TBS and TBDPS respectively, followed by selective deprotection and oxidation of the hydroxy group at C1, proved to be the optimal choice. This route allowed us to introduce at C2 a group resistant to the conditions for the deprotection of the OH at C8. Thus, sequential treatment of compound **14** with TBSCl and TBDPSCl, followed by AcOH in THF/H_2O[18] provided compound **17**. TEMPO oxidation,[19] and coupling with NH_4Cl in DMF[20] furnished amide **19**. One-pot hydrogenation of the alkene and cleavage of the PMB group[21] gave the target key fragment **20** in 73% yield. EDC-mediated esterification of the aliphatic chain **20** with the dehydroproline fragment **5** afforded compound **21**.

Due to the instability of dehydroproline core in acidic medium, the protecting groups were sequentially removed under mild, aprotic conditions. After several attempts, we found that careful treatment with $TiCl_4$ at -20 °C,[22] followed by TBAF mediated desilylation, gave promysalin (-)-**1** with absolute configuration 2*R*, 8*R*, 16*S*.

When this work was in its final stage, Wuest and coworkers[3] published an elegant total synthesis of all promysalin stereoisomers and assigned the absolute configuration (2*R*, 8*R*, 16*S*) to the natural compound.

Wuest's synthesis of the aliphatic chain appears more efficient than ours, giving the 2,8-dihydroxymyristamide moiety in 45% overall yield from 5-hexenoic acid over 6 steps. On the contrary, their approach to the synthesis of the salicyldehydroproline fragment appears less straightforward, requiring 7 steps from methyl salicylate to obtain the SEM-protected acid for coupling with the alcohol moiety.

The combination of the two routes would most likely offer the best pathway to a convergent synthesis of the natural compound and could be easily transposed to a large scale. The combined strategy could also be optimal for the preparation of promysalin analogues for SAR studies and further exploration of the intriguing modes of action of this compound.[3]

3. Conclusions

In summary, a total synthesis of the antibiotic Promysalin was designed and carried out. Crucial steps for our strategy included a MacMillan asymmetric α-hydroxylation of carbonyl compounds applied for the construction of the myristamide framework, and a lactam reduction by Superhydride ® to obtain the salicyldehydroproline fragment. Because of the modular nature of the synthesis, work is in progress to prepare analogues for biological evaluation.

4. Experimental section

4.1. General Information

All reagents and solvents were reagent grade or were purified by standard methods before use. Melting points were determined in open capillaries by a SMP3 apparatus and are uncorrected. ^{1}H spectra were recorded on Bruker AMX 300 MHz and Bruker AV600 spectrometers. TMS was used as an internal standard and the chemical shifts were reported in parts per million (δ). The peak patterns are indicated as follows: s, singlet; d, doublet; dd, doublet of doublet; t, triplet; m, multiplet; q, quartet. The coupling constants, J are reported in Hertz (Hz). and ^{13}C NMR spectra were recorded on Bruker AMX 300 MHz and Bruker AV600 spectrometers. Optical rotations were measured with a Perkin Elmer 241 polarimeter.. IR spectra were recorded on a Perkin Elmer 1310 spectrophotometer and reported in wave numbers (cm^{-1}).. The elemental analyses

were recorded with a CARLO ERBA EA 1108 instrument. Solvents were routinely distilled prior to use; anhydrous tetrahydrofuran (THF) and ether (Et_2O) were obtained by distillation from sodium-benzophenone ketyl; dry methylene chloride was obtained by distillation from phosphorus pentoxide. All reactions requiring anhydrous conditions were performed under a positive nitrogen flow and all glassware were oven dried and/or flame dried. Isolation and purification of the compounds were performed by flash column chromatography on silica gel 60 (230-400 mesh). Analytical thin-layer chromatography (TLC) was conducted on TLC plates (silica gel 60 F_{254}, aluminum foil). Compounds on TLC plates were detected under UV light at 254 and 365 nm or were revealed spraying with 10% phosphomolybdenic acid (PMA) in ethanol.

4.2. Experimental procedures and spectroscopic data

4.2.1. Ethyl (S)-1-(2-((2-methoxyethoxy)methoxy)benzoyl)-5-oxopyrrolidine-2-carboxylate **(3)**. Ghosez's reagent (1-chloro-*N*,*N*,2-trimethyl-1-propenylamine) (2.5 mL, 0.02 mol) was added dropwise to a solution of 2-((2-methoxyethoxy)methoxy)benzoic acid[5] (4.1 g, 0.02 mol) in dry dichloromethane (40 mL) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue was dried under vacuum and used in the next step without purification. In another 2-necked dry flask was placed ethyl L-pyroglutamate (1.4 g, 9.2 mmol) in dry toluene (15 mL) and the solution was cooled to 0 °C. To this was added NEt_3 (3.2 mL, 0.02 mol) followed by dropwise addition of the crude acid chloride solution in toluene (15 mL). The reaction mixture was heated at 80 °C for 3 h, and then it was cooled to room temperature and quenched by addition of saturated aqueous $NaHCO_3$ (30 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 100 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the residue by flash column chromatography in 0-18% acetone : hexane gave **3** (2.75 g, 82%) as a yellow gummy solid; R_f (20% acetone : hexane, double run) = 0.30. $[\alpha]_D^{23}$ = +30.9 (*c* 1.0, $CHCl_3$); ν_{max} (thin film) : 3045, 1760, 1700, 1620, 1510, 1470, 1340, 1280, 1250, 1210, 1120, 1010, 750, 710 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.40 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 7.5 Hz, 1H), 7.05 (dd, *J* = 7.5, 7.5 Hz, 1H), 5.27 (d, *J* = 7.0 Hz, AB, 1H), 5.23 (d, *J* = 7.0 Hz, AB, 1H), 4.91 (dd, *J* = 2.9, 9.5 Hz, 1H), 4.28 (q, *J* = 7.3 Hz, 2H), 3.80 (t, *J* = 4.5 Hz, 2H), 3.55 (t, *J* = 4.5 Hz, 2H), 3.38 (s, 3H), 2.73-2.64 (m, 1H), 2.55-2.50 (m, 1H), 2.50-2.45 (m, 1H), 2.2-2.10 (m, 1H), 1.33 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 172.8, 170.9, 167.8, 154.5, 131.8, 128.4,

125.8, 121.6, 114.5, 93.9, 71.6, 67.7, 61.7, 58.9, 58.2, 31.6, 21.7, 14.1 ppm. Elemental analysis calcd (%) for $C_{18}H_{23}NO_7$: C 59.17, H 6.34, N 3.83; Found: C 59.38, H 6.32, N 3.84.

4.2.2. Ethyl (S)-1-(2-((2-methoxyethoxy)methoxy)benzoyl)-2,3-dihydro-1H-pyrrole-2-carboxylate **(4)**.

To a stirred solution of **3** (1.1 g, 3.0 mmol) in dry toluene (22 mL) was added Superhydride ® (3.6 mL, 3.6 mmol, 1 M in THF) at -78 °C under N_2 atmosphere. The solution was stirred for 1 h at -78 °C, then DMAP (7 mg, 0.06 mmol) and DIPEA (2.8 mL, 0.02mol) were added, followed by very slow addition of TFAA (0.5 mL, 3.6 mmol) over 5 min. The reaction mixture was gradually warmed to room temperature and stirred for 3 h. Water (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 75 mL); the combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified using flash column chromatography in 0-50 % ethyl acetate: hexane to give **4** (650 mg, 62%) as a yellow oil; R_f (35% ethyl acetate: hexane) = 0.30. $[\alpha]_D^{23}$ = -104.3 (*c* 1.00, $CHCl_3$); ν_{max} (liquid film) : 3050-2800 (br), 1760, 1660, 1640, 1620, 1510, 1470, 1425, 1250, 1210, 1110, 1045, 1000, 860, 780 cm^{-1}. 1H NMR (300 MHz, $CDCl_3$): δ = 7.41-7.34 (m, 2H,), 7.23 (d, *J* = 7.8 Hz, 1H), 7.07 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.2 (m, 1H), 5.30 (s, 2H), 5.10-5.03 (m, 1H), 5.00 (dd, *J* = 3.6, 10.5 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 3.86-3.81 (m, 2H,), 3.57-3.52 (m, 2H), 3.37 (s, 3H), 3.18-3.13 (m, 1H,), 2.74-2.69 (m, 1H), 1.33 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 170.8, 164.9, 153.4, 131.2, 130.8, 128.8, 125.9, 122.1, 115.3, 108.5, 93.7, 71.5, 67.9, 61.3, 59.0, 58.0, 34.1, 14.1 ppm. Elemental analysis calcd (%) for $C_{18}H_{23}NO_6$: C 61.88, H 6.64, N 4.01; found: C 62.01, H 6.62, N 4.00.

4.2.3. (S)-1-(2-((2-methoxyethoxy)methoxy)benzoyl)-2,3-dihydro-1H-pyrrole-2-carboxylicacid **(5)**.

A solution of **4** (920 mg, 2.6 mmol) in EtOH (22.5 mL) was cooled to 0 °C. To this was added dropwise a solution of LiOH (166 mg, 3.9 mmol) in water (11.25 mL). After complete addition the reaction mixture was warmed to room temperature and stirred for 5 h. EtOH was removed *in vacuo,* the aqueous layer was washed with 40 % ethyl acetate in diethyl ether (2 × 25 mL), cooled to 0 °C and acidified using 5% citric acid. The product was extracted using 5% methanol : dichloromethane (3 × 100 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated to afford pyrroline-carboxylic acid **5** (809 mg, 97%) as a pale yellow gummy solid; R_f (5% methanol : dichloromethane) = 0.35. $[\alpha]_D^{23}$ = -97.6 (*c* 1.00, $CHCl_3$); ν_{max} (thin film) 3300-2900 (br), 1760, 1660, 1640, 1625, 1505, 1475, 1440,

1292, 1005, 760, 725 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.38 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.35 (d, *J* = 7.9 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.05 (dd, *J* = 7.9, 7.9 Hz, 1H), 6.62 (brs, 1H), 6.09 (d, *J* = 2.2 Hz, 1H), 5.28-5.25 (m, 2H), 5.17-5.22 (m, 1H), 5.08 (dd, *J* = 4.9, 10.1 Hz, 1H), 3.80-3.76 (m, 2H), 3.52 (t, *J* = 4.7 Hz, 2H), 3.34 (s, 3H), 3.08-3.02 (m, 2H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 172.2, 167.1, 153.4, 131.8, 129.7, 128.8, 124.8, 122.1, 115.1, 111.2, 93.7, 71.5, 68.0, 58.9, 53.4, 32.9 ppm. Elemental analysis calcd (%) for $C_{16}H_{19}NO_6$: C 59.81, H 5.96, N 4.36, found: C 59.99, H 5.94, N 4.35.

4.2.4. (R)-octane-1,2-diol (**7**).

A suspension of L-proline (322 mg, 2.8 mmol) in $CHCl_3$ (30 ml) was cooled to 4 °C and stirred for 15 min, then nitrosobenzene (3 g, 0.03 mol) was added in one portion. At this time the solution turned green. To this suspension was added octanal (13.1 ml, 84.0 mmol) in one portion. The resulting solution was then stirred at 4 °C for 2 h and it turned yellow. The reaction mixture was then added dropwise to an ethanol (25 mL) suspension of $NaBH_4$ (1.05 g, .0.03 mol) at 0 °C. After 30 min, the reaction was treated with saturated aqueous $NaHCO_3$ (50 mL). The aqueous layer was extracted with dichloromethane (3 ×75 mL); the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. To a solution of the oxy-aniline adduct (14.6 g) in EtOH/AcOH (3:1, 156 mL), Zn dust (8.1 g, 0.12 mol) was added portionwise. The resulting suspension was stirred at room temperature for 1 h. The reaction mixture was filtered through a plug of celite and the residue was washed with ethanol (50 mL); the filtrate was concentrated *in vacuo* at a temperature <40 °C. The residue was dissolved in ethyl acetate (200 mL) and washed with saturated aqueous $NaHCO_3$ solution (100 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting yellow oil was purified using flash column chromatography (eluent: 20-50% ethyl acetate : hexane) to afford (*R*)-octane-1,2-diol **7** (3.7 g, 91%) as an off-white sticky solid; R_f (50% ethyl acetate : hexane) = 0.35. $[\alpha]_D^{23}$ = +14.1 (*c* 1.00, MeOH); ν_{max} (liquid film) 3600-3300 (br), 3100, 1550, 1490, 1445, 1290, 1130, 950 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 3.76-3.70 (m, 1H), 3.67 (dd, *J* = 3.2, 11.1 Hz, 1H), 3.45 (dd, *J* = 7.9, 11.1 Hz, 1H), 2.50-2.35 (m, 2H), 1.49-1.26 (m, 10H), 0.90 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 72.3, 66.8, 33.2, 31.7, 29.3, 25.5, 22.6, 14.0 ppm. Elemental analysis calcd (%) for $C_8H_{18}O_2$: C 65.71, H 12.41; found: C 65.50, H 12.44.

4.2.5. (R)-2-(4-methoxybenzyloxy)octan-1-ol (**9**).

A solution of (*R*)-octane-1,2-diol **7** (7.4 g, 0.05 mol), PPTS (254 mg, 1.1 mmol) in dry dichloromethane (126 mL) was cooled to 0 °C. 4-Methoxybenzaldehyde dimethylacetal (12.9

mL, 0.08 mol) was added dropwise. The reaction mixture was stirred at room temperature for 2 h under N_2 atmosphere. Excess NEt_3 (10 mL) was added, and then the reaction mixture was concentrated *in vacuo*. The product was filtered through a short pad of silica gel (neutralized with 5 % NEt_3 in hexane) in 1% ethyl acetate: hexane to afford (*R*)-4-hexyl-2-(4-methoxyphenyl)-1,3-dioxolane **8**. (16 g of crude compound, mixture of diastereomers.) as a yellow oil; R_f (5% ethyl acetate : hexane) = 0.55. Compound **8** was unstable, thus it was used immediately in the next step without further purification.

To a stirred solution of **8** (16.0 g, crude) in dry dichloromethane (300 mL), DIBAL (90.90 mL, 0.09 mol, 1 M in dichloromethane) was added dropwise at -78 °C under N_2 atmosphere and stirred for 2 h at -78 °C. The reaction mixture was gradually warmed to -20 °C over 1 h, methanol (5 mL) was added dropwise and the resulting solution was stirred for 5 min. Dilution with diethyl ether (150 mL) followed by addition of saturated aqueous solution of Rochelle's salt (150 mL) gave a thick suspension which was stirred vigorously until the two layers become clear. The organic layer was separated; and the aqueous layer was extracted with ethyl acetate (3 × 150 ml). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification using flash column chromatography in 0-12% ethyl acetate: hexane gave **9** (9.7 g, 72% over two steps) as a pale yellow oil. R_f (15% ethyl acetate : hexane) = 0.46. $[\alpha]_D^{23}$ = -17.5 (*c* 1.00, $CHCl_3$); ν_{max} (liquid film) 3650-3300 (br), 1640, 1620, 1540, 1495, 1370, 1205, 1100, 850 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ = 7.30 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.58 (d, *J* = 11.4 Hz, AB, 1H), 4.49 (d, *J* = 11.4 Hz, AB, 1H), 3.74-3.68 (s, 3H), 3.70 (m, 1H), 3.55-3.48 (m, 2H), 2.00 (brs, 1H), 1.70-1.62 (m, 1H), 1.55-1.48 (m, 1H), 1.39-1.25 (m, 8H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 159.3, 130.6, 129.4 (× 2), 113.9 (× 2); 79.5, 71.2, 64.3, 55.3, 31.8, 30.8, 29.5, 25.4, 22.6, 14.1 ppm. Elemental analysis calcd (%) for $C_{16}H_{26}O_3$: C 72.14, H 9.84; found: C 72.39, H 9.81.

4.2.6. (R)-2-(4-methoxybenzyloxy)octanal **(10)**.

To a stirred solution of oxalyl chloride (8.8 mL, 0.10 mol) in dry dichloromethane (286 mL), was added DMSO (9.7 mL, 0.14 mol) in dry dichloromethane (143 mL) dropwise at -78 °C under N_2 atmosphere. Stirring was continued for 15 min, then **9** (9.1 g, 0.03 mol) in dry dichloromethane (143 mL) was added dropwise. After complete addition, the reaction mixture was stirred at -78 °C for 1 h, then NEt_3 (47 mL, 0.34 mol) was added dropwise. The reaction mixture was gradually warmed to 0 °C and stirred at this temperature until complete conversion was observed. The mixture was diluted with diethyl ether (50 mL) and poured in cold sat. $NaHCO_3$ (140 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (3 × 100 mL).

The combined organic extracts were washed with brine (75 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification using flash column chromatography in 0-5% ethyl acetate: hexane gave aldehyde **10** (8.5 g, 94%) as a colorless oil. R_f (4% ethyl acetate : hexane) = 0.47. $[\alpha]_D^{23}$ = +37.8 (*c* 0.75, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ= 9.63 (d, *J* = 2.3 Hz, 1H), 7.30 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 4.62 (d, *J* = 11.8 Hz, AB, 1H), 4.50 (d, *J* = 11.4 Hz, AB, 1H), 3.82 (s, 3H), 3.78-3.72 (m, 1H), 1.71-1.63 (m, 2H), 1.49-1.20 (m, 8H), 0.91 (t, J = 7.1 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 204.1, 159.5, 129.7 (×2), 129.4, 113.9 (×2), 83.2, 72.2, 55.2, 31.6, 30.0, 29.0, 24.7, 22.5, 14.0 ppm. Elemental analysis calcd (%) for $C_{16}H_{24}O_3$: C 72.69, H 9.15; found: C 72.92, H 9.12.

4.2.7. (R)-Z-8-(4-methoxybenzyloxy)tetradec-6-enyloxy)tert-butyldimethylsilane **(11)**.

To a stirred suspension of $TBSO(CH_2)_6P^+Ph_3Br^-$[12] (11.85 g, 0.021 mol) in anhydrous THF (76 mL) cooled to -78 °C, *n*-BuLi (12.35 mL, 0.02 mol, 1.6 M in hexane) was added. The brown red coloured suspension obtained was stirred at -78 °C for 30 min under N_2 atmosphere. Compound **10** (4.0 g, 0.01mol) in anhydrous THF (76 mL) was added dropwise; on complete addition the solution turned pale yellow. The reaction mixture was stirred at -78 °C for 15 min, warmed to room temperature and stirred for 2 h. After addition of saturated NH_4Cl (100 mL), the product was extracted with diethyl ether (3 × 100 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash column chromatography in 0-1% ethyl acetate: hexane yielded **11** (5.2 g, 74%) as a colorless oil; R_f (1% ethyl acetate : hexane) = 0.36. $[\alpha]_D^{23}$ = +15.6 (*c* 1.00, $CHCl_3$). ν_{max} (liquid film) 3050, 1570, 1550, 1535, 1480, 1290, 1110, 860, 760, 730 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ= 7.24 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.59 (dt, *J* = 11.0, 7.3 Hz, 1H), 5.29 (dd, *J* = 11.0, 9.4 Hz, 1H), 4.49 (d, *J* = 11.6 Hz, AB, 1H), 4.24 (d, *J* = 11.6 Hz, AB, 1H), 4.12-4.02 (m, 1H), 3.80 (s, 3H), 3.60 (t, *J* = 6.4 Hz, 2H), 2.12-1.95 (m, 2H), 1.73-1.18 (m, 16H), 0.89 (m, 12 H), 0.05 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 23 °C) δ= 158.9, 133.1, 131.2 (×2), 129.2 (×2), 113.6 (×2), 73.8, 69.4, 63.1, 55.2, 35.8, 32.7, 31.8, 29.6, 29.3, 27.8, 26.0 (×3), 25.5, 25.4, 22.6, 18.3, 14.1, -5.3 (×2) ppm. Elemental analysis calcd (%) for $C_{28}H_{50}O_3Si$: C 72.67, H 10.89; found: C 72.40, H 10.92.

4.2.8. (R)-8-(4-methoxybenzyloxy)tetradec-6-en-1-ol **(12)**.

A solution of TBS ether **11** (9.5 g, 0.02 mol) in anhydrous THF (82 mL) was cooled to 0 °C. TBAF (61 mL, 0.06 mol, 1 M in THF) was added at 0 °C under N_2 atmosphere. The reaction mixture was warmed to room temperature and stirred for 1 h. Saturated NH_4Cl (125 mL) was

added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 × 150 mL), and the combined organic extracts were washed with brine (80 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified using flash column chromatography in 0-15% ethyl acetate: hexane to afford desired **12** (6.3 g, 88%) as a pale yellow oil; R_f (15% ethyl acetate: hexane) = 0.41. $[\alpha]_D^{23}$ = +20.0 (*c* 1.00, $CHCl_3$). ν_{max} (liquid film) 3600-3200 (br), 3090, 3020, 1640, 1530, 1480, 1320, 1290, 1280, 1105, 1050, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.61 (dt, *J* = 11.0, 7.3 Hz, 1H), 5.31 (dd, *J* = 11.0, 9.5 Hz, 1H), 4.51 (d, *J* = 11.9 Hz, AB, 1H), 4.27 (d, *J* = 11.9 Hz, AB, 1H), 4.15-4.05 (m, 1H), 3.82 (s, 3H), 3.65 (t, *J* = 6.4 Hz, 2H), 2.15-2.00 (m, 2H), 1.75-1.50 (m, 4H), 1.48-1.30 (m, 12H), 0.88 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 158.9, 133.0, 131.2, 131.1, 129.2 (×2), 113.7 (×2), 73.8, 69.3, 62.8, 55.3, 35.7, 32.6, 31.8, 29.5, 29.3, 27.8, 25.4, 25.4, 22.6, 14.1 ppm. Elemental analysis calcd (%) for $C_{22}H_{36}O_3$: C 75.82, H 10.41; found: C 75.60, H 10.43.

4.2.9. (R)-8-(4-methoxybenzyloxy)tetradec-6-enal **(13)**.

To a stirred solution of oxalyl chloride (4.7 mL, 0.05 mol) in dry dichloromethane (150 mL), a solution of DMSO (5.1 mL, 0.07 mol) in dry dichloromethane (75 mL) was added dropwise at -78 °C under N_2 atmosphere and stirred for 15 min. Tetradecanol **12** (6.3 g, 0.02 mol) in dry dichloromethane (75 mL) was added dropwise. After complete addition, the reaction mixture was stirred at -78 °C for 1 h. After addition of NEt_3 (25 mL, 0.18 mol), the reaction mixture was gradually warmed to 0 °C and stirred at this temperature until complete conversion was observed. The mixture was diluted with diethyl ether (50 mL) and poured in cold sat. $NaHCO_3$ (80 mL), the organic layer was separated and aqueous layer was extracted with diethyl ether (3 × 150 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification using flash column chromatography with 0-5% ethyl acetate : hexane gave **13** (5.7 g, 91%) as a colorless oil; R_f (3% ethyl acetate : hexane) = 0.44. $[\alpha]_D^{23}$ = +17.8 (*c* 1.00, CH_3OH). ^1H NMR (300 MHz, $CDCl_3$) δ = 9.78 (s, 1H), 7.25 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 5.59 (dt, *J* = 11.0, 7.3 Hz, 1H), 5.34 (dd, *J* = 11.0, 9.5 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, AB, 1H), 4.26 (d, *J* = 11.3 Hz, AB, 1H), 4.012-4.02 (m, 1H), 3.82 (s, 3H), 2.44 (t, *J* = 7.3 Hz, 2H), 2.12-1.98 (m, 2H), 1.73-1.56 (m, 4H), 1.49-1.35 (m, 4H), 1.32-1.18 (m, 6H), 0.89 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, MeOD) δ= 200.3, 159.4, 133.2, 130.7, 129.3, 129.1, 113.5, 113.3, 104.6, 73.4, 69.2, 54.4, 35.5, 32.3, 31.8, 29.4, 29.1, 27.6, 25.2, 24.1, 22.5, 13.2 ppm. Elemental analysis calcd (%) for $C_{22}H_{34}O_3$: C 76.26, H 9.89; found: C 75.98, H 9.87.

4.2.10. (2R,8R)-8-(4-methoxybenzyloxy)tetradec-6-ene-1,2-diol **(14)**.

A suspension of L-proline (57.6 mg, 0.5 mmol) in $CHCl_3$ (16.5 mL) was cooled to 4 °C and stirred for 15 min, then nitrosobenzene (525 mg, 5 mmol) was added in one portion. At this time the solution turned green. To this suspension was added a solution of tetradecanal **13** (3.4 g, 9.9 mmol) in $CHCl_3$ (16.5 mL) in one portion. The resulting solution was then stirred at 4 °C for 2 h. At this time the solution turned yellow. The reaction mixture was then added to an ethanol (50 mL) suspension of $NaBH_4$ (374 mg, 9.9 mmol) at 0 °C. After 30 min. the reaction was treated with saturated aqueous $NaHCO_3$ (125 mL). The aqueous layer was extracted with dichloromethane (3 × 150 mL). The combined organic extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The oxy-aniline adduct (4.1 g) was dissolved in EtOH/AcOH (3:1, 30 mL) and Zn dust (1.2 g, 0.02 mol) was added portionwise. The resulting suspension was stirred at room temperature for 1 h. The reaction mixture was filtered through a plug of celite and the residue was washed with ethanol (25 mL). The filtrate was concentrated *in vacuo* at <40 °C. The residue was dissolved in ethyl acetate (200 mL) and washed with a saturated $NaHCO_3$ solution (100 mL), brine (50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting yellow oil was purified using flash column chromatography with 20% - 50% ethyl acetate : hexane to afford 1,2 diol **14** (2.78 g 77%) as a yellow oil; R_f (40% ethyl acetate : hexane) = 0.36. $[\alpha]_D^{23}$ = +18.9 (*c* 1.00, $CHCl_3$); ν_{max} (liquid film) 3600-3200 (br), 3090, 1640, 1540, 1482, 1090, 1070, 760, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.23 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.56 (dt, *J* = 11.0, 7.3 Hz, 1H), 5.32 (dd, *J* = 11.0, 9.5 Hz, 1H), 4.49 (d, *J* = 11.4 Hz, AB, 1H), 4.25 (d, *J* = 11.4 Hz, AB, 1H), 4.12-4.02 (m, 1H); 3.79 (s, 3H), 3.71-3.53 (m, 2H), 3.45-3.35 (m, 1H), 2.88 (brs, 1H), 2.26 (brs, 1H), 2.15-1.95 (m, 2H), 1.73-1.15 (m, 14H), 0.87 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 132.8, 131.6, 131.1, 129.4 (×2), 113.8 (×2), 73.9, 72.2, 69.5, 66.8, 55.4, 35.8, 32.8, 31.9, 29.4, 27.8, 25.8, 25.5, 22.7, 14.2 ppm. Elemental analysis calcd (%) for $C_{22}H_{36}O_4$: C 72.49, H 9.95, found: C 72.70, H 9.94.

4.2.11.(2R,8R)-Z-1-((tert-butyldimethylsilyl)oxy)-8-(4-methoxybenzyloxy)tetradec-6-en-2-ol **(15)**.

To a stirred solution of tetradecane 1,2 diol **14** (400 mg, 1.1 mmol) in dry dichloromethane (11 mL) was added imidazole (149 mg, 2.2 mmol), then TBSCl (215 mg, 1.4 mmol) was added portionwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 6 h, then it was quenched by addition of ice; the aqueous layer was extracted with dichloromethane (2 × 30 mL). The combined organic extracts were washed with brine (20 mL), dried over anhydrous

Na_2SO_4 and concentrated *in vacuo.* The residue was purified using flash column chromatography (0 - 8% ethyl acetate : petroleum ether) to afford mono TBS ether **15** (518 mg, 98%) as a colorless oil; R_f (5% ethyl acetate : hexane) = 0.35. $[\alpha]_D^{23}$ = +14.3 (*c* 1.00, $CHCl_3$); ν_{max} (liquid film) 3610, 3580-3400 (br), 1625, 1605, 1530, 1480, 1260, 1120, 1090, 1050, 850, 795 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ7.26 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.61 (dt, *J* = 11.0, 7.3 Hz, 1H), 5.33 (dd, *J* = 11.0, 9.5 Hz, 1H), 4.51 (d, *J* = 11.3 Hz, AB, 1H), 4.26 (d, *J* = 11.3 Hz, AB, 1H), 4.12-4.02 (m, 1H), 3.82 (s, 3H), 3.69-3.59 (m, 2H), 3.40 (dd, *J* = 8.5, 10.4 Hz, 1H), 2.17-1.96 (m, 2H), 1.74-1.11 (m, 14H), 0.92 (s, 9H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.09 (s, 6H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.1, 132.9, 131.6, 131.2, 129.3 (×2), 113.8 (×2), 73.9, 71.7, 69.5, 67.3, 55.4, 35.9, 32.5, 32.0, 29.4, 27.9, 26.0 (×3), 25.9, 25.5, 22.7, 18.4, 14.2, -5.2, -5.3 ppm. Elemental analysis calcd (%) for $C_{28}H_{50}O_4Si$: C 70.24, H 10.53; found: C 70.01, H 10.54.

4.2.12.(R)-5-((R)-Z-6-((4-methoxybenzyl)oxy)dodec-4-en-1-yl)-2,2,8,8,9,9-hexamethyl-3,3-diphenyl-4,7-dioxa-3,8-disiladecane **(16)**.

A solution of mono TBS ether **15** (518 mg, 1.1 mmol), imidazole (220 mg, 3.2 mmol) in dry DMF (5.4 mL) was cooled to 0 °C. TBDPS-Cl (0.42 mL, 1.6 mmol) was added dropwise at 0 °C. After complete addition, the reaction mixture was stirred at room temperature under N_2 atmosphere for 12 h. TLC showed partial completion of reaction, thus another (302 mg, 1.1 mmol of TBDPS-Cl was added and stirred for further 8 h. The reaction was quenched by addition of ice; the aqueous layer was extracted with diethyl ether (3 × 50 mL), then the combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified using flash column chromatography with 0-3% ethyl acetate: petroleum ether) to afford bis-silyl ether **16** (773 mg, 98%) as a yellow oil; R_f (2% ethyl acetate : hexane) = 0.47. $[\alpha]_D^{23}$ = +5.5 (*c* 1.2, $CHCl_3$). ν_{max} (liquid film) 3100, 1630, 1520, 1480, 1265, 1120, 850, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ = 7.76-7.65 (m, 4H), 7.47-7.31 (m, 6H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.5 Hz, 2H), 5.51 (dt, *J* = 11.0, 7.0 Hz, 1H), 5.27 (dd, *J* = 11.0, 9.5 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, AB, 1H), 4.21 (d, *J* = 11.6 Hz, AB, 1H), 4.011-4.01 (m, 1H), 3.81 (s, 3H), 3.85-3.71 (m, 1H), 3.53-3.38 (m, 2H), 2.00-1.84 (m, 2H), 1.65-1.20 (m, 14H), 1.06 (s, 9H), 0.89 (t, *J* = 7.0 Hz, 3H), 0.83 (s, 9H), 0.06 (s, 3H), 0.01 (s, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 159.1, 136.0 (×6), 134.6, 134.5, 133.3, 131.3, 129.7, 129.4, 127.6 (×5), 113.7 (×2), 74.1, 73.6, 69.6, 66.3, 55.4, 35.9, 33.6, 32.0, 29.5, 28.1, 27.2 (×3), 26.0 (×3), 25.5, 24.8, 22.8, 19.5, 18.4, 14.3, -5.3 (×2) ppm. Elemental analysis calcd (%) for $C_{44}H_{68}O_4Si_2$: C 73.69, H 9.56: found: C 73.50, H 9.55.

4.2.13.(2R,8R)-Z-2-((tert-butyldiphenylsilyl)oxy)-8-((4-methoxybenzyl)oxy)tetradec-6-en-1-ol **(17)**.

A mixture of bis-silyl ether **16** (698 mg, 0.9 mmol) in AcOH/ THF/ H_2O 3 : 1: 1 (36 mL) was stirred at room temperature for 36 h. The reaction was quenched by addition of saturated aq. K_2CO_3 (50 mL), followed by addition of solid K_2CO_3. The aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo.* Purification using flash column chromatography with 0-8% ethyl acetate: petroleum ether produced **17** (500 mg, 92%) as a yellow oil; R_f (5% ethyl acetate : hexane) = 0.56. $[\alpha]_D^{23}$ = -18.07 (*c* 1.3, $CHCl_3$); ν_{max} (liquid film) 3610, 3580-3300 (br), 1635, 1600, 1530, 1480, 1445, 1270, 1120, 840, 760, 730 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ= 7.75-7.58 (m, 4H); 7.49-7.32 (m, 6H); 7.21 (d, *J* = 8.6 Hz, 2H); 6.85 (d, *J* = 8.6 Hz, 2H); 5.41 (dt, *J* = 11.2, 7.4 Hz, 1H); 5.24 (dd, *J* = 11.2, 9.6 Hz, 1H); 4.44 (d, *J* = 11.4 Hz, AB, 1H); 4.18 (d, *J* = 11.4 Hz, AB, 1H); 4.07-3.95 (m, 1H); 3.79 (s, 3H,); 3.80-3.72 (m, 1H); 3.58-3.41 (m, 2H); 1.91-1.73 (m, 2H); 1.66-1.13 (m, 14H); 1.07 (s, 9H); 0.87 (t, *J* = 7.0 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ= 159.1, 136.0 (×2), 135.8 (×2), 134.0, 133.8, 132.7, 131.5, 131.2, 129.9 (×2), 129.3 (×2), 127.9 (×4), 113.8 (×2), 1C overlapped to the solvent signal, 74.0, 69.5, 66.0, 55.4, 35.8, 33.3, 31.9, 29.4, 27.8, 27.2 (×4), 25.5, 22.7, 19.5, 14.2 ppm. Elemental analysis calcd (%) for $C_{38}H_{54}O_4Si$: C 75.70, H 9.03; found: C 75.42, H 9.00.

4.2.14. (2R,8R)-Z-2-((tert-butyldiphenylsilyl)oxy)-8-((4-methoxybenzyl)oxy)tetradec-6-enoic acid **(18)**.

A suspension of **17** (340 mg, 0.6 mmol), $NaHCO_3$ (141 mg, 1.7 mmol) in acetonitrile / water (3.4 mL:3.4 mL) was cooled to 0 °C and stirred for 10 min. TEMPO (17 mg, 0.1 mmol), and bis(acetoxy)iodobenzene (451 mg, 1.4 mmol), were added in one portion and the solution was stirred at 0 °C for 4 h. Saturated aq. $NaHCO_3$ (20 mL) was added at 0 °C and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude oil was purified using flash column chromatography (0-20% ethyl acetate: petroleum ether) to furnish **18** (259 mg, 70%) as a colorless oil; R_f (20% ethyl acetate : hexane) = 0.43. $[\alpha]_D^{23}$ = +5.9 (*c* 1.00, MeOH). ν_{max} (liquid film) 3100-2800 (br), 1730, 1630, 1605, 1525, 1480, 1445, 1280, 1260, 1125, 845, 760, 720 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.70-7.53 (m, 4H), 7.51-7.31 (m, 6H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 5.48-5.38 (m, 1H), 5.27 (m, 1H), 4.43 (d, *J* = 11.4 Hz, AB, 1H), 4.340-4.32 (m, 1H), 4.16 (d, *J* = 11.4 Hz, AB, 1H), 4.08-3.92 (m, 1H), 3.79 (s, 3H), 1.95-1.18 (m, 16H), 1.12 (s, 9H), 0.86 (t, *J* = 6.7 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$)

δ = 174.8, 159.1, 135.8 (×4), 135.4, 132.9, 132.4, 131.8, 131.1, 130.5, 130.3, 129.3 (×2), 127.9 (×4), 113.8 (×2), 73.9, 72.9, 69.5, 55.4, 35.8, 34.3, 31.9, 29.8, 29.4, 27.4, 27.0 (×3), 25.4, 22.7, 19.4, 14.2 ppm. Elemental analysis calcd (%) for $C_{38}H_{52}O_5Si$: C 73.98, H 8.50; found: C 74.22, H 8.52.

4.2.15. (2R,8R)-Z-2-((tert-butyldiphenylsilyl)oxy)-8-((4-methoxybenzyl)oxy)tetradec-6-enamide **(19)**.

A solution of **18** (224 mg, 0.4 mmol), NH_4Cl (38 mg, 0.7 mmol) in dry DMF (5 mL) was cooled to 0 °C. HOBT (73 mg, 0.5 mmol) and HBTU (205 mg, 0.5 mmol) were added followed by DIPEA (0.23 mL, 1.4 mmol). The reaction mixture was warmed to room temperature and stirred for 1 h. Ice was added, and then the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were washed with cold brine (3× 10 mL) and dried over Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified using flash column chromatography (0-30% ethyl acetate : petroleum ether) to furnish **19** (180 mg, 73%) as a white sticky solid; R_f (25% ethyl acetate : hexane) = 0.45. $[\alpha]_D^{23}$ = -8.9 (*c* 1.4, CH_3OH). ν_{max} (thin film) 3550, 3505, 3450, 3100, 1700, 1635, 1605, 1580, 1540, 1485, 1450, 1285, 1135, 850, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.73-7.54 (m, 4H), 7.50-7.30 (m, 6H), 7.20 (d, *J* = 8.2 Hz, 2H), 6.85 (d, *J* = 8.2 Hz, 2H), 6.73 (brs, 1H), 5.78 (brs, 1H), 5.50-5.39 (m, 1H), 5.32-5.22 (m, 1H), 4.43 (d, *J* = 11.4 Hz, AB, 1H), 4.33.4.25 (m, 1H), 4.17 (d, *J* = 11.4 Hz, AB, 1H), 3.98 (m, 1H), 3.80 (s, 3H), 1.94-1.83 (m, 2H), 1.75-1.15 (m, 14H), 1.12 (s, 9H), 0.87 (t, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 177.7, 160.5, 137.3 (×2), 137.1 (×2), 134.4, 134.0, 133.1, 132.7, 131.8 (×2), 130.8 (×2), 129.5 (×4), 115.3 (×2), 75.5 (×2), 71.0, 56.8, 37.3, 35.6, 33.4, 31.3, 30.9, 29.0, 28.6 (×3), 26.9, 25.1, 24.2, 20.8, 15.7 ppm. Elemental analysis calcd (%) for $C_{38}H_{53}NO_4Si$: C 74.10, H 8.67, N 2.27; found: C 74.38, H 8.69, N 2.26.

4.2.16. (2R,8R)-2-((tert-butyldiphenylsilyl)oxy)-8-hydroxytetradecanamide **(20)**.

To a solution of **19** (68 mg, 0.11 mmol) in methanol (6 mL) was added 10% Pd/C (20 mg). The suspension was evacuated under vacuum and flushed with H_2 gas (4 times). The reaction mixture was stirred under H_2 atmosphere for 12 h at room temperature, then filtered through a plug of celite and the residue was washed with ethyl acetate (10 mL). The filtrate was concentrated *in vacuo* and purified using flash column chromatography (0-40% ethyl acetate: petroleum ether to obtain **20** (40 mg, 73%) as a pale yellow oil; R_f (30% ethyl acetate : hexane) = 0.35. $[\alpha]_D^{23}$ = -10.1 (*c* 1.0, CH_3OH). ν_{max} (thin film) 3550, 3505, 3450, 3100, 1710, 1604, 1575, 1450, 1299, 930, 790, 740 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ= 7.70-7.54 (m, 4H), 7.50-7.31 (m, 6H), 6.72

(brs, 1H), 5.67 (brs, 1H), 4.27 (t, *J* = 4.6 Hz, 1H), 3.60-3.50 (m, 1H), 1.94-1.55 (m, 2H), 1.48-1.15 (m, 19H), 1.12 (s, 9H), 0.89 (t, *J* = 6.6 Hz, 3H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ = 176.6, 135.8 (×4), 133.1, 132.6, 130.3 (×2),128.0 (×4), 74.4, 72.0, 37.5, 34.5, 32.0, 29.5, 27.2, 27.1 (×3), 25.7 (×2), 23.5, 22.8 (×2), 19.4, 14.1 ppm. Elemental analysis calcd (%) for $C_{30}H_{47}NO_3Si$: C 72.38, H 9.52, N 2.80; found: C 72.19, H 9.54, N 2.79.

4.2.17. (7R,13R)-14-amino-13-((tert-butyldiphenylsilyl)oxy)-14-oxotetradecan-7-yl (S)-1-(2-((2-methoxyethoxy)methoxy)benzoyl)-2,3-dihydro-1H-pyrrole-2-carboxylate **(21)**.

To a stirred solution of pyrrolinecarboxylic acid **5** (66 mg, 0.2 mmol) in dry dichloromethane (8 mL) was added EDC (52 mg, 0.3 mmol) and DMAP (5 mg, 0.04 mmol) at 0 °C. A solution of **20** (69 mg, 0.14 mmol) in dichloromethane (2 mL) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and stirred for 16 h, then it was poured into water (10 mL) and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 25 mL) and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo* and the residue was purified using flash column chromatography (FCC) with 0-40% ethyl acetate: hexane to furnish **21** (56 mg, 50%) as a pale yellow oil; R_f (40% ethyl acetate : hexane) = 0.35. $[\alpha]_D^{23}$ = -44.9 (*c* 1.0, MeOH); ν_{max} (liquid film) 3520, 3410, 3090, 1760, 1710, 1660, 1640, 1440, 1280, 1130, 1010, 920, 790 cm^{-1}. ^{1}H NMR (600 MHz, acetone-d_6) (mixture of conformers) δ= 7.74-7.65 (m, 4H), 7.53-7.41 (m, 7H), 7.31 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.14-7.08 (m, 1H), 6.97 (brs, 1H), 6.72 (brs, 1H), 6.22-6.18 (m, 1H), 5.30 (s, 2H), 5.114-5.10 (m, 1H), 4.95- 4.87 (m, 2H), 4.16 (t, *J* = 5.1 Hz, 1H), 3.80 (t, *J* = 4.8 Hz, 2H), 3.51 (t, *J* = 4.8 Hz, 2H), 3.27 (s, 3H), 3.20-3.12 (m, 1H), 2.70-2.55 (m, 1H), 2.20-1.92 (m, 2H), 1.67-1.11 (m, 18H), 1.11 (s, 9H), 0.87 (t, *J* = 7.3 Hz, 3H) ppm. ^{13}C NMR (150 MHz, acetone-d_6,) δ = 175.1, 170.5, 164.1, 153.5, 135.7 (×2), 135.6 (×2), 133.3, 132.8, 131.0, 130.7, 130.0, 129.5, 128.6, 127.8 (×4), 126.5, 121.8, 115.5, 108.1, 93.7, 74.5, 74.3, 71.4, 67.9, 58.1, 57.9, 34.5, 34.0, 34.0, 33.8, 31.5, 29.6, 29.5, 26.5 (×3), 25.0, 24.7, 23.4, 22.3, 18.9, 13.4 ppm. Elemental analysis calcd (%) for $C_{46}H_{64}N_2O_8Si$: C 68.97, H 8.05, N 3.50; found: C 69.20, H 8.03, N 3.52.

4.2.18. (7R,13R)-14-amino-13-hydroxy-14-oxotetradecan-7-yl-(S)-1-(2-hydroxybenzoyl)-2,3-dihydro-1H-pyrrole-2-carboxylate **(1)**.

To a stirred solution of **21** (28 mg, 0.03 mmol) in dichloromethane (1 mL) was added $TiCl_4$ (0.13 mL, 0.13 mmol, 1 M in dichloromethane) at -20 °C. The reaction mixture was stirred at -20 °C for 10 min; then aqueous ammonia (2 mL) was added. The aqueous layer was extracted with

ethyl acetate (2 × 30 mL), and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. The solvent was removed *in vacuo*. The crude compound (24 mg) was dissolved in dry THF (1 mL) and cooled to 0 °C. TBAF (0.1 mL, 0.1 mmol, 1 M in THF) was added dropwise. The reaction mixture was warmed to room temperature and stirred for 1 h, then saturated NH_4Cl (5 mL) was added. The aqueous layer was extracted with ethyl acetate (2 × 25 mL); and the combined organic extracts were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After removal of the solvent *in vacuo*, the residue was purified using preparative TLC in 5% methanol : dichloromethane) to furnish **1** (10 mg, 70% over two step) as a colorless oil; R_f (3% methanol : dichloromethane) 0.33. $[\alpha]_D^{23}$ = -33.4 (*c* 1.00, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$) δ= 9.53 (brs, 1H), 7.40-7.34 (m, 2H), 6.97 (d, *J* = 8.2 Hz, 1H), 6.89 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.70 (brs, 1H), 6.59 (brs, 1H), 5.42 (brs, 1H), 5.36-5.26 (m, 1H), 5.00 (dd, *J* = 4.7, 11.3 Hz, 1H), 5.02-4.95 (m, 1H), 4.08 (dd, *J* = 3.6, 8.1 Hz, 1H), 3.60-3.40 (m, 1H), 3.12 (ddd, *J* = 17.1, 11.3, 2.5 Hz, 1H), 2.68 (m, 1H), 1.98-1.08 (m, 20H), 0.85 (t, *J* = 6.8 Hz, 3H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ = 177.0, 171.3, 167.4, 158.0, 133.4, 130.8, 128.3, 119.4, 118.0, 117.8, 111.0, 76.0, 71.4, 59.3, 34.5, 34.3, 34.1, 33.6, 31.8, 29.2, 28.3, 25.5, 24.8, 24.5, 22.6, 14.1 ppm. Elemental analysis calcd (%) for $C_{26}H_{38}N_2O_6$: C 65.80, H 8.07, N 5.90; found: C 66.02, H 8.05, N 5.91.

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Supplementary data

Supplementary data (^1H and ^{13}C NMR spectra of all compounds) associated with this article can be found at.

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