Total Synthesis of Salicylihalamides A and B

Christian Herb, Alexander Bayer, and Martin E. Maier*[a]

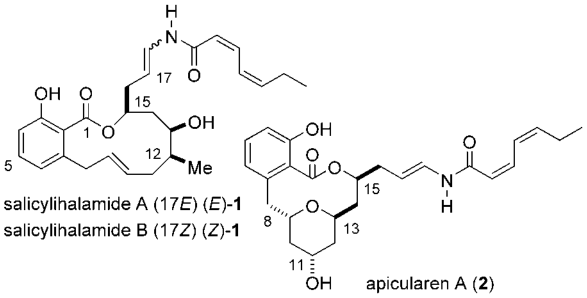
Dedicated to Professor J. Mulzer on the occasion of his 60th birthday

Abstract: The paper illustrates two efficient routes to macrolactone **19** containing a 3-(*para*-methoxybenzyloxy)propyl side chain at C-15. The chiral center at C-15 was introduced by a Noyori reduction of keto ester **5**. The intermediate common to both routes, aldehyde **8**, was prepared from keto ester **5**. The subsequent chain extension utilized Evans aldol reactions. The first route leads to the alkene **14**, which was used, after hydroboration, for a Suzuki cross-coupling reaction with vinyl iodide **15**. The derived seco acid **18** was converted into the macrolactone **19** by a Mitsunobu lactonization by using immobilized triphenylphosphine. Alternatively, an aldol reaction of **8** with the 4-pentenoyl derivative **20** was used to prepare alkene **26**. This building block led to ester **28**, which could also be converted into macrolactone **19** by the classical ring-closing metathesis. After conversion of the C-15 side chain to the corresponding aldehyde, the enamide was introduced through hemiaminal formation and formal elimination of water. Separation of the double-bond isomers and removal of the silyl protecting groups provided salicylihalamides A (*E*)-**1** and B (*Z*)-**1**.

Keywords: antitumor agents • lactonization • metathesis • salicylihalamide • total synthesis

Introduction

Secondary metabolites that contain a benzolactone ring have been known for some time. Typical examples include zearalenone,[1] radicicol,[2] C292,[3] the pochonins,[4] and queenslandon.[5] While the biosynthetic pathways to these compounds are quite similar, they show a broad spectrum of biological activity. Recently, the structural diversity of this class of natural products was widened with the discovery of the benzolactone enamides.[6] In addition to the benzolactone part, these compounds feature an enamide side chain. The additional enamide side chain makes these natural products powerful antitumor compounds. Their initial biological targets seem to be mammalian vacuolar adenosine triphosphatase (V-ATPase) enzymes.[7] Recent studies show that salicylihalamide binds to the V_0 and not the V_1 sector of the V-ATPases.[8] These membrane-bound enzymes are responsible for controlling the pH value in vacuoles and the cytoplasm. Depending on the cell type studied, other effects such as phosphorylation of mitogen-activated protein kinases or antiangiogenic effects were observed. Prototypical examples of the benzolactone enamides are salicylihalamide A and apicularen A (Scheme 1). The salicylihalamides were isolated from the sponge *Haliclona* sp.,[9] whereas apicularen A has been discovered in various myxobacteria strains.[10]



Scheme 1. Structures of two important benzolactone enamides.

Both of these natural products are unique in their own right. Thus, the macrolactone double bond in salicylihalamide A is striking since it is in an allylic position relative to the aromatic ring. On the other hand, the unique feature of apicularen A is the ether bridge that spans the macrolactone ring. The challenging structural features of these natural products combined with their novel mode of action have stimulated a number of synthesis programs. So far, total syn-

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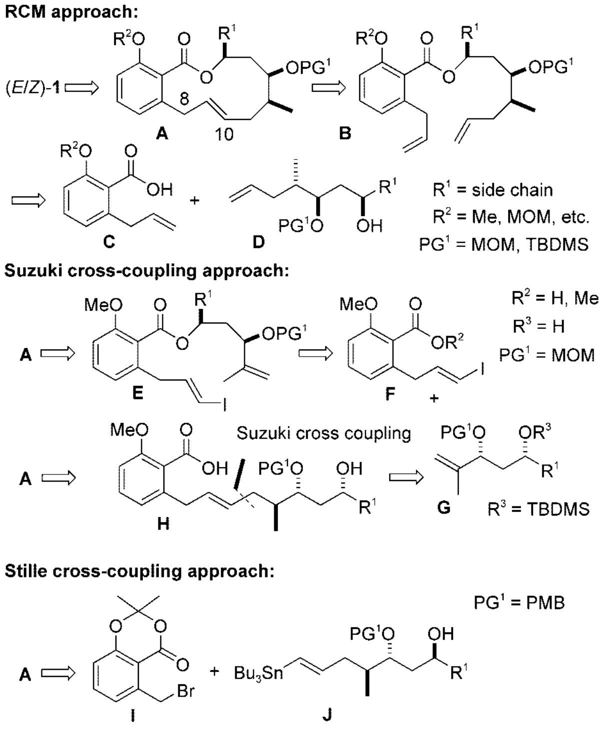
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.

DOI: 10.1002/chem.200400617

theses for the salicylihalamides[11] and apicularen A[12] have been described. In addition, formal total syntheses[13,14] and synthetic studies have been published.[15]

A synthesis of salicylihalamide basically has to address three issues. First, the building-block synthesis has to provide the three stereocenters. Then, in order to form the macrolactone ring, the best one of several strategies should be chosen. Finally, an efficient method for attachment of the enamide side chain is required. The known syntheses of the macrolactone ring of salicylihalamide can be summarized as follows (Scheme 2). In several cases, a Mitsunobu esterification was used to combine a benzoic acid, containing the allyl group, with a secondary alcohol that contains all the stereocenters and a terminal alkene. Macrocyclization of ester **B** was then achieved by ring-closing metathesis. In our group we developed two complementary routes to the core structure of salicylihalamide A.[13b,15e] In both cases the ester is formed by Mitsunobu reaction and the *trans*-alkene is created by a Suzuki cross-coupling reaction between a vinyl iodide **F** and an alkylborane, with the latter being generated from **G** by a diastereoselective hydroboration. The two approaches only differ by the order of the events. In the synthesis of the Rizzacasa group, the two key building blocks **I** and **J** are combined by a Stille coupling of a vinyl stannane with a benzyl bromide. Macrolactonization is accomplished by intramolecular attack of an alkoxide on an acetal ester.[13a]

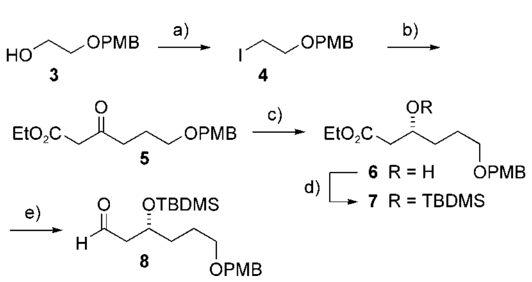


Scheme 2. General approaches to the macrolactone core of the salicylihalamides. RCM = ring-closing metathesis, MOM = methoxymethyl, TBDMS = *tert*-butyldimethylsilyl, PMB = *para*-methoxybenzyl.

The length of the side chain that extends from C-15 depends very much on the way the enamide is attached. In cases where the enamide is fashioned by nucleophilic addition to a vinyl isocyanate or by cross-coupling between a vinyl iodide and the unsaturated amide, the side chain is two carbon atoms long. In this paper we show that macrolactone **19** containing a three-carbon side chain can be converted into salicylihalamides A and B by reaction of the corresponding aldehyde with the unsaturated amide **34**. Macrolactone **19** was reached either by the Suzuki cross-coupling/intramolecular Mitsunobu strategy or by the intermolecular Mitsunobu/ring-closing metathesis tactic. It turned out that both routes are of more or less similar efficiency if one neglects the provision of the aromatic building blocks.

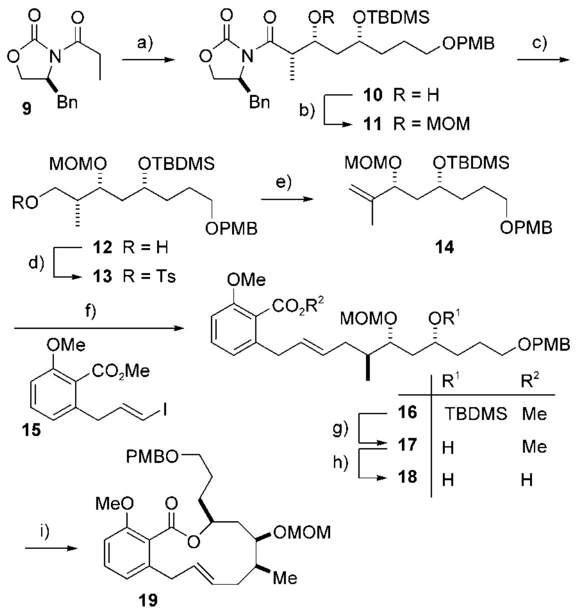
Results

As a common precursor to both routes we used the chiral β-alkoxyaldehyde **8**. The synthesis of this aldehyde started from the monoprotected ethylene glycol[16] **3** which was converted into the iodide **4** (Scheme 3) by using a combination of iodine and triphenylphosphine.[17] Due to the somewhat unstable nature of **4**, this compound was used immediately in a Weiler alkylation[18] of ethyl acetoacetate to provide the β-keto ester **5**. Reduction of the keto group under Noyori conditions[19,20] with (*R*)-(+)-BINAP as the chirality inducer gave the β-hydroxyestor **6** in good yield and with good optical purity (82 %, 95 % *ee*). After protection of the secondary alcohol moiety with TBDMSOTf/2,6-lutidine,[21] the resulting ester **7** was reduced with DIBAL to give the desired aldehyde **8**.

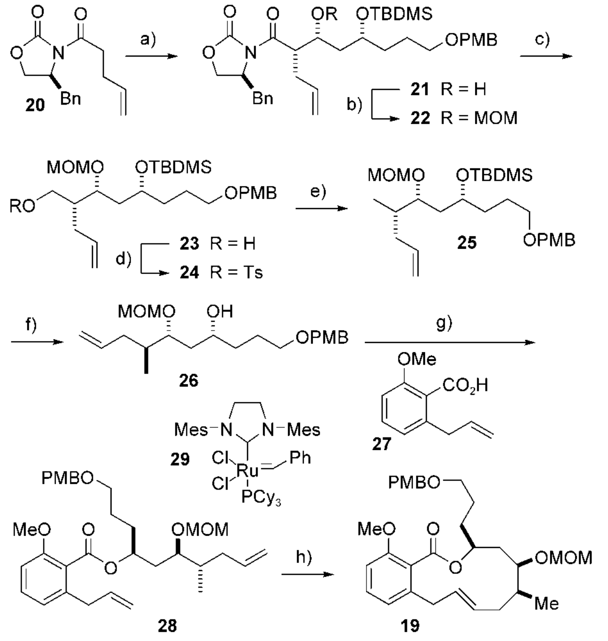


Scheme 3. Synthesis of the protected hydroxy aldehyde **8**. a) PPh$_3$ (1.01 equiv), imidazole (2 equiv), I$_2$ (1.01 equiv), THF, 0°C, 1 h, 97 %; b) NaH (1.2 equiv), ethyl acetoacetate, THF, *n*BuLi (1.2 equiv), −50°C, 30 min, then add iodide **4** (1 equiv), 95 %; c) [RuCl$_2$(PhH)]$_2$ (0.003 equiv), (*R*)-(+)-BINAP (0.07 equiv), DMF, 90°C, 20 min, then add to **5** in EtOH, H$_2$ (4 bar), 90°C, 20 h, 82 %, 95 % *ee*; d) TBDMSOTf (1.12 equiv), 2,6-lutidine (2.5 equiv), CH$_2$Cl$_2$, $0\rightarrow23$°C, 1 h, 100 %; e) DIBAL (1.2 equiv), CH$_2$Cl$_2$, −78°C, 2 h, 83 %. BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, TBDMSOTf = *tert*-butyldimethylsilyltriflate, DIBAL = diisobutylaluminum hydride.

In order to enter the Suzuki cross-coupling route, aldehyde **8** was subjected to an Evans aldol reaction under Crimmins conditions[22] (1.05 equiv of TiCl$_4$, 2.5 equiv of diamine) with the propionyloxazolidinone[23] **9** (Scheme 4). This gave the *syn*-aldol product **10** in good yield. Protection of the secondary alcohol as a MOM ether was followed by reductive removal of the chiral auxiliary.[24] In order to introduce the terminal double bond, the primary alcohol **12** was



Scheme 4. Synthesis of the macrolactone **19** by Suzuki cross-coupling and intramolecular Mitsunobu reaction. a) $TiCl_4$ (1.05 equiv), TMEDA (2.5 equiv), CH_2Cl_2, 0 °C, then add aldehyde **8** (1.1 equiv), 0 °C, 1 h, 78 %; b) *i*Pr_2NEt (20 equiv), $MeOCH_2Cl$ (10 equiv), Bu_4NI (0.1 equiv), 0→23 °C, 12 h, 86 %; c) $NaBH_4$ (5 equiv), H_2O/THF (1:2), 0 to 23 °C, 12 h, 80 %; d) TsCl (3 equiv), pyridine, 0 °C, 5 h, 100 %; e) NaI (2.5 equiv), DBU (5 equiv), glyme, reflux, 3 h, 89 %; f) 9-BBN (1.5 equiv), THF, 0→23 °C, 12 h, then add $[PdCl_2(dppf)]$ (0.1 equiv), vinyl iodide **15** (0.9 equiv), 3 N NaOH (3 equiv), 40 °C, 4 h, 84 %; g) TBAF (3 equiv), THF, 0→23 °C, 48 h, 100 %; h) THF/EtOH/H_2O (4:8:8), $LiOH{\cdot}H_2O$, (10 equiv), 70 °C, 3 d, 92 %; i) PS-PPh_3 (5 equiv), THF, 15 min, then add DEAD (2 equiv), 0→23 °C, 72 %. TMEDA = *N,N,N′,N′*-tetramethyl-1,2-ethanediamine, Ts = tosyl = toluene-4-sulfonyl, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, 9-BBN = 9-borabicyclo[3.3.1]nonane, dppf = 1,1′-bis(diphenylphosphanyl)ferrocene, TBAF = tetrabutylammonium fluoride, PS = polystyrene, DEAD = diethylazodocarboxylate.

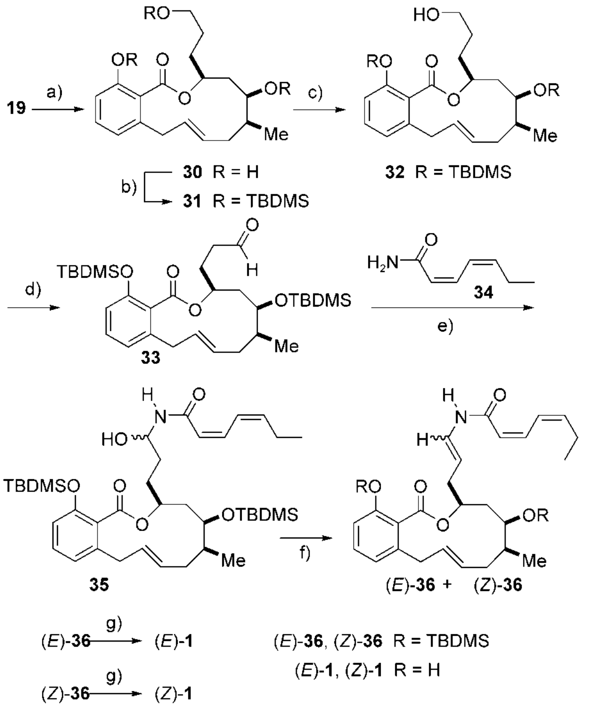


Scheme 5. Synthesis of the macrolactone **19** by Mitsunobu esterification and ring-closing metathesis. a) $TiCl_4$ (1.05 equiv), (−)-spartein (2.5 equiv), CH_2Cl_2, 0 °C, add aldehyde **8** (1.1 equiv), 0 °C, 1 h, 68 %; b) *i*Pr_2NEt (20 equiv), $MeOCH_2Cl$ (10 equiv), Bu_4NI (0.1 equiv), 0→23 °C, 3 d, 82 %; c) $NaBH_4$ (5 equiv), H_2O/THF (1:2), 0→23 °C, 12 h, 86 %; d) TsCl (3 equiv), pyridine, 0 °C, 12 h, 95 %; e) Et_3BHLi (3.6 equiv), THF, 0→23 °C, 15 h, 95 %; f) TBAF (3 equiv), THF, 0→23 °C, 48 h, 99 %; g) Ph_3P (2.5 equiv), acid **27** (5 equiv), DIAD (2.55 equiv), toluene, 23 °C, 3 h, 71 %; h) Grubbs catalyst **29** (0.1 equiv), toluene, 70 °C, 2 h, 75 % of (*E*)-**19** and 12 % of (*Z*)-**19**. DIAD = diisopropylazodicarboxylate.

converted into the tosylate **13**. Elimination to form alkene **14** was smoothly accomplished by heating tosylate **13** in the presence of NaI and DBU.[25] In this way, alkene **14** could be produced in gram quantities. The methyl-bearing stereocenter from the aldol reaction was intentionally destroyed to allow for its reintroduction with the opposite stereochemistry by a diastereoselective hydroboration reaction.[26] The intermediate borane resulting from treatment of **14** with 9-BBN was added to a solution of the vinyl iodide[13b] **15** in THF containing aqueous NaOH and $[PdCl_2(dppf)]$. This led to the *trans*-alkene **16** in high yield. Treatment of **16** with TBAF in THF caused cleavage of the silyl ether group. The methyl ester moiety of **17** was cleaved with LiOH to give rise to the seco acid **18**. Based on our previous experience with the macrolactonization of a related substrate, the Mitsunobu macrolactonization was run in the presence of immobilized triphenylphosphine. In this way, macrolactone **19** was obtained in 72 % yield from the hydroxy acid **18**. We found that the yields for the Suzuki cross-coupling and the macrolactonization were somewhat higher with the longer side chain, an observation that is difficult to rationalize.

While this synthesis of macrolactone **19** is quite effective, concise, and stereoselective, we also wanted to compare it directly to the ring-closing metathesis strategy, the quasi standard method for forming the salicylihalamide core structure. An aldol reaction of aldehyde **8** with the pentenoyloxazolidinone[27] **20** by using the proven Crimmins conditions gave the *syn*-aldol product **21** (Scheme 5). In order to reach the *anti* stereochemistry of the vicinal methyl- and hydroxy-bearing stereocenters, the acyl group of the aldol product **21** had to be reduced to a methyl group.[11,28] Prior to this, the secondary alcohol was protected with MOM chloride to give **22**. Reductive removal of the chiral auxiliary, tosylation of the primary alcohol group of **23**, and substitution of the tosylate moiety of **24** with hydride by using super hydride gave the aliphatic chain **25**. After cleavage of the silyl ether protecting group, the resulting secondary alcohol **26** was combined with benzoic acid[11g] **27** by a Mitsunobu esterification. The dienyl ester **28** was subjected to a ring-closing metathesis[29] by using the second-generation Grubbs catalyst[30] **29** (0.1 equiv, 1 mM in toluene at 70 °C). This led to a mixture of the desired *E* isomer (*E*)-**19** (75 %) and the *Z* isomer (*Z*)-**19** (12 %). Similar ratios for the ring-closing metathesis have been observed by other groups.[6] The two diastereomers could be separated by flash chromatography. From the aldehyde **8** this sequence requires eight steps (22.8 % overall yield). While the Suzuki coupling/macrolactonization strategy requires nine steps, the overall yield (26.6 %) is somewhat higher.

With two efficient routes to the key macrolactone **19** in hand, the total synthesis of salicylihalamide was targeted. The successful realization of this task relied on our ability to convert an aldehyde into an enamide.[31] First, all ether groups of **19** were cleaved by treatment with 9-iodoborobicyclononane[32] (Scheme 6). The rather polar crude triol **30** was completely silylated to give macrolactone **31** (60% for 2 steps). A subsequent selective desilylation[33] with CSA in a mixture of methanol and CH$_2$Cl$_2$ led to the primary alcohol **32**. Oxidation of **32** to form aldehyde **33** was accomplished with TPAP.[34] The enamide side chain could be attached by treating aldehyde **33** with the aluminum carboximidoate derived from the amide[31] **34** and DIBAL.[35] This furnished the hemiaminal **35** in 61% yield as a 1:1 mixture of diastereomers, together with 32% recovered aldehyde. The formal elimination of water from **35** was achieved by heating a THF solution of **35** containing acetic anhydride and pyridine to reflux. These conditions resulted in a separable mixture of the *E*/*Z*-enamides (*E*)-**36** (45%) and (*Z*)-**36** (14%). Finally, both enamides were deprotected with HF in pyridine[11d] to give the natural products salicylihalamide A (75%) and salicylihalamide B (69%), respectively.



Scheme 6. Synthesis of salicylihalamides A and B from the macrolactone **19**. a) 9-I-9-BBN (1.9 equiv), CH$_2$Cl$_2$, 23 °C, 90 s; b) TBDMSCl, (35 equiv), imidazole (44 equiv), DMAP (1.8 equiv), DMF, 23 °C, 4 d, 60% over 2 steps; c) CSA (0.2 equiv), CH$_2$Cl$_2$/MeOH, 0 °C, 1.5 h, 85%; d) TPAP (0.125 equiv), NMO (1.45 equiv), CH$_2$Cl$_2$, 0 °C, 1 h, 91%; e) dienamide **34** (2 equiv), DIBAL (2.54 equiv), THF, 0 °C, 30 min, then add aldehyde **33** (1 equiv), 0 °C, 14 h, 61% of **35** and 32% of **33**; f) pyridine (30 equiv), Ac$_2$O (15 equiv), THF, 23 °C, 24 h, then reflux, 48 h, 45% of (*E*)-**36** and 14% of (*Z*)-**36**; g) HF·pyridine (2.2 M in THF/pyridine, 5.4:1), 23 °C, 3 d, 75% of (*E*)-**1**, 69% of (*Z*)-**1**. DMAP = 4-dimethylaminopyridine, (±)-CSA = (±)-camphorsulfonic acid, TPAP = tetra-*n*-propylammonium perruthenate, NMO = 4-methylmorpholine *N*-oxide.

Conclusion

In summary, we illustrated two efficient routes to the macrolactone **19** containing a 3-(*para*-methoxybenzyloxy)propyl side chain at C-15. The chiral center at C-15 was introduced by a Noyori reduction of keto ester **5**. The intermediate common to both routes, aldehyde **8**, was extended by Evans aldol reactions. The first route leads to the alkene **14**, which was used, after hydroboration, for a Suzuki cross-coupling reaction with vinyl iodide **15**. The derived seco acid **18** was converted into macrolactone **19** by a Mitsunobu lactonization with immobilized triphenylphosphine. Alternatively, an aldol reaction of **8** with the 4-pentenoyl derivative **20** was used to prepare alkene **26**. From this building block, ester **28** was prepared; this could be converted into macrolactone **19** by a classical ring-closing metathesis. After conversion of the C-15 side chain to form the corresponding aldehyde **33**, the enamide was introduced through hemiaminal formation and formal elimination of water. With the great diversity potential of the aldehyde function, a number of salicylihalamide side-chain analogues should now be accessible.

Experimental Section

General: ^{1}H and ^{13}C NMR: Bruker Avance 400 spectrometer; spectra were recorded at 295 K, either in CDCl$_3$, C$_6$D$_6$, or CD$_3$OD; chemical shifts are calibrated to the residual proton and carbon resonances of the solvent: CDCl$_3$ (δH = 7.25, δC = 77.0 ppm), C$_6$D$_6$ (δH = 7.16, δC = 128.0 ppm), or CD$_3$OD (δH = 3.30, δC = 49.0 ppm); NMR spectroscopy peaks were assigned according to the numbering by Boyd et al.[9]. IR: Jasco FT/IR-430 apparatus. Optical rotation: Jasco P-1020 polarimeter; reported in degrees; $[\alpha]_D$ (*c* [g/100 mL], solvent); recorded at 298 K. MS: Finnigan Triple-Stage-Quadrupole TSQ-70 (ionizing voltage of 70 eV) or Intectra AMD 402 mass spectrometers. HRMS: Intectra AMD MAT-711A (EI) or Bruker Daltonic APEX 2 (ESI) mass spectrometers. Flash chromatography: J. T. Baker silica gel, 43–60 µm. Thin-layer chromatography: Macherey–Nagel Polygram Sil G/UV$_{254}$ plates. All solvents used in the reactions were distilled before use. Dry diethyl ether, tetrahydrofuran, and toluene were distilled from sodium and benzophenone, whereas dry dichloromethane, dimethylformamide, pyridine, and triethylamine were distilled from CaH$_2$. Petroleum ether with a boiling range of 40–60 °C was used. Reactions were generally run under an argon atmosphere. All commercially available compounds were used as received, unless stated otherwise.

1-[(2-Iodoethoxy)methyl]-4-methoxybenzene (4): A solution of alcohol[16] **3** (8.00 g, 43.9 mmol) in THF (80 mL) was treated with PPh$_3$ (11.63 g, 44.3 mmol) and imidazole (5.98 g, 87.8 mmol) and then cooled to 0 °C. Iodine (11.25 g, 44.3 mmol) was added in 3 portions and the mixture was stirred for 1 h while it warmed to room temperature. The solution was transfered to a round-bottom flask containing a suspension of silica gel (200 g) in THF (300 mL) and the solvent was removed completely in vacuo. The residue was chromatographed over a short pad of silica gel (elution with petroleum ether/ethyl acetate, 2:1) to provide the iodide **4** (12.43 g, 97%) as a light-yellow oil.

Ethyl 6-[(4-methoxybenzyl)oxy]-3-oxohexanoate (5): A solution of ethyl 3-oxobutanoate (3.89 mL, 4.00 g, 30.7 mmol) in THF (40 mL) was added dropwise to a cooled (−20 °C) suspension of NaH (0.89 g, 36.9 mmol) in THF (30 mL). After gas evolution had stopped, the solution was stirred at room temperature for 30 min and then recooled to −50 °C. The cooled solution was treated with *n*-butyllithium (15.0 mL, 37.5 mmol, 2.5 M in hexane) and stirred for a further 30 min before a solution of iodide **4** in THF (40 mL) was added dropwise. The cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction was then quenched by treatment with saturated aqueous NH$_4$Cl solution. The phases were separated and the aqueous layer extracted twice with diethyl ether (50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution and dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude product was chromatographed over silica gel to produce the β-keto ester **5** (8.59 g; 95 %) as a light-yellow oil. $R_f=0.47$ (petroleum ether/ethyl acetate, 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.27$ (t, $J=7.2$ Hz, 3H; Et CH_3), 1.90 (tt, $J=6.1$, 7.1 Hz, 2H; H-5), 2.65 (t, $J=7.1$ Hz, 2H; H-4), 3.43 (s, 2H; H-2), 3.46 (t, $J=6.1$ Hz, 2H; H-6), 3.80 (s, 3H; PMB CH_3), 4.18 (q, $J=7.2$ Hz, 2H; Et CH_2), 4.40 (s, 2H; PMB CH_2), 6.88 (d, $J=8.6$ Hz, 2H; PMB H-3,5), 7.24 ppm (d, $J=8.6$ Hz, 2H; PMB-H-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.0$ (Et CH_3), 23.6 (C-5), 39.7 (C-4), 49.2 (C-2), 55.2 (OCH_3), 61.2 (Et CH_2), 68.6 (C-6), 72.4 (PMB CH_2), 113.7 (PMB C-3,5), 129.2 (PMB C-2,6), 130.3 (PMB C-1), 159.1 (PMB C-4), 167.2 (C-1), 202.6 ppm (C-3); IR (film): $\tilde{\nu}=1033$, 1097, 1248, 1303, 1514, 1715 cm^{-1}; MS (EI): m/z (%): 292 (4), 156 (13), 136 (45), 135 (73), 121 (38), 111 (72), 86 (60), 84 (100), 77 (24); HRMS (ESI): calcd for $C_{16}H_{22}NaO_5$ $[M+\mathrm{Na}]^+$: 317.13594; found: 317.13578.

Ethyl (3*R*)-3-hydroxy-6-[(4-methoxybenzyl)oxy]hexanoate (6): Dry, degassed DMF (3 mL) was added to a flask containing benzene ruthenium(II) chloride dimer (43 mg, 0.09 mmol) and (*R*)-(+)-BINAP (116 mg, 0.19 mmol). The slurry was heated to 90 °C with stirring for 20 min. The reddish brown solution was allowed to cool to room temperature and then added through a cannula to a Parr hydrogenation bomb containing a degassed solution of β-keto ester **5** (8.31 g, 28.2 mmol) in dry, degassed ethanol (15 mL). The hydrogenation bomb was flushed a few times with hydrogen and then kept under a hydrogen pressure of 4.0 bar at 90 °C with vigorous shaking for 20 h. After cooling to room temperature the dark-red solution was concentrated in vacuo and the residue was purified by flash chromatography to provide β-hydroxy ester **6** (6.88 g, 82 %, 95 % *ee*) as a pale-yellow oil. The enantioselectivity was determined by chiral HPLC and was found to be 97.5:2.5 with the desired isomer favored. $R_f=0.24$ (petroleum ether/ethyl acetate, 2:1); HPLC: t_R (R enantiomer) = 9.1 min, t_R (S enantiomer) = 12.0 min on a CHIRA-GROM 4 column, 8 μm, 60 × 2 mm (corresponds to CHIRACEL AS) with *n*-heptane/*i*PrOH 89:11, 0.1 mL min^{-1} flow; $[\alpha]_D=-8.0$ ($c=1.32$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.25$ (t, $J=7.2$ Hz, 3H; Et CH_3), 1.47–1.63 (m, 2H; H-4), 1.63–1.81 (m, 2H; H-5), 2.41 (dd, $J=16.2$, 8.2 Hz, 1H; H-2a), 2.47 (dd, $J=16.2$, 4.2 Hz, 1H; H-2b), 3.29 (br s, 1H; OH), 3.47 (t, $J=6.1$ Hz, 2H; H-6), 3.78 (s, 3H; PMB CH_3), 4.01 (dddd, $J=8.2$, 8.1, 4.4, 4.2 Hz, 1H; H-3), 4.15 (q, $J=7.2$ Hz, 2H; Et CH_2), 4.42 (s, 2H; PMB CH_2), 6.86 (d, $J=8.6$ Hz, 2H; PMB H-3,5), 7.24 ppm (d, $J=8.6$ Hz, 2H; PMB H-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.1$ (Et CH_3), 25.9 (C-5), 33.6 (C-4), 41.5 (C-2), 55.2 (PMB CH_3), 60.5 (Et CH_2), 67.7 (C-3), 69.8 (C-6) 72.5 (PMB CH_2), 113.7 (PMB C-3,5), 129.2 (PMB C-2,6), 130.3 (PMB C-1), 159.1 (PMB C-4), 172.7 ppm (C-1); IR (film): $\tilde{\nu}=1248$, 1302, 1372, 1514, 1612, 1732, 2859, 2937, 3449 cm^{-1}; MS (EI): m/z (%): 297 (10), 296 (17), 278 (22), 241 (8), 203 (9), 190 (12), 160 (11), 142 (37), 137 (88), 121 (100), 109 (19), 99 (18), 91 (9), 77 (10); HRMS (EI): calcd for $C_{16}H_{24}O_5$ $[M]^+$: 296.1623; found: 296.1675.

Ethyl (3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-6-[(4-methoxybenzyl)oxy]-hexanoate (7): 2,6-Lutidine (2.11 mL, 1.94 g, 18.1 mmol) and TBDMSOTf (2.32 mL, 2.67 g, 8.71 mmol) were added to a stirred solution of β-hydroxy ester **6** (2.15 g, 7.26 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C. The resulting solution was stirred for 1 h and allowed to warm to room temperature. After adding water (70 mL), the phases were separated and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with 1 N HCl (30 mL) and brine (30 mL), dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography to yield the protected alcohol **7** (2.98 g, 100 %) as a slightly yellow oil. $R_f=0.71$ (petroleum ether/ethyl acetate, 5:1); $[\alpha]_D=-10.0$ ($c=1.31$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.02$, 0.04 (2 × s, 3H each; $Si(CH_3)_2$), 0.85 (s, 9H; $SiC(CH_3)_3$), 1.24 (t, $J=7.1$ Hz, 3H; Et CH_3), 1.51–1.69 (m, 4H; H-4, H-5), 2.39 (dd, $J=14.7$, 5.6 Hz, 1H; H-2a), 2.44 (dd, $J=14.7$, 7.1 Hz, 1H; H-2b), 3.42 (t, $J=6.4$ Hz, 2H; H-6), 3.79 (s, 3H; PMB CH_3), 4.10 (qd, $J=7.1$, 2.1 Hz, 2H; Et CH_2), 4.10–4.18 (m, 1H; H-3), 4.41 (s, 2H; PMB CH_2), 6.86 (d, $J=8.5$ Hz, 2H; PMB H-3,5), 7.24 ppm (d, $J=8.5$ Hz, 2H; PMB H-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.9$ ($Si(CH_3)_2$), -4.6 ($Si(CH_3)_2$), 14.2 (Et CH_3), 17.9 (SiC), 25.2 (C-5), 25.7 ($C(CH_3)_3$), 34.1 (C-4), 42.7 (C-2), 55.2 (PMB CH_3), 60.3 (Et CH_2), 69.2 (C-3), 70.0 (C-6) 72.4 (PMB CH_2), 113.7 (PMB C-3,5), 129.2 (PMB C-2,6), 130.6 (PMB C-1), 159.1 (PMB C-4), 171.7 ppm (C-1); IR (film): $\tilde{\nu}=1038$, 1096, 1173, 1204, 1249, 1302, 1362, 1464, 1472, 1514, 1613, 1737, 2856, 2930, 2954 cm^{-1}; MS (EI): m/z (%): 347 (7), 189 (8), 149 (22), 147 (24), 121 (100), 77 (7), 75 (16), 73 (19); HRMS (ESI): calcd for $C_{22}H_{38}NaO_5Si$ $[M+\mathrm{Na}]^+$: 433.23807; found: 433.23809.

(3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-[(4-methoxybenzyl)oxy]hexanal (8): DIBAL (1.0 M in hexane, 2.92 mL) was added dropwise to a stirred solution of ester **7** (1.00 g, 2.44 mmol) in dry CH_2Cl_2 (25 mL) over 10 min at −78 °C. After the reaction had been stirred for 2 h at −78 °C, methanol (0.7 mL) was added, the cooling bath was removed, and the mixture was allowed to warm to room temperature. H_2O (5 mL) was then added and the mixture was extracted with Et_2O (3 × 15 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/diethyl ether, 2:1) to yield aldehyde **8** (0.74 g, 83 %) as a pale-yellow oil. $R_f=0.46$ (petroleum ether/ethyl acetate, 5:1); $[\alpha]_D=-0.9$ ($c=1.09$, CH_2Cl_2)^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.04$, 0.05 (2 × s, 3H each; $Si(CH_3)_2$), 0.86 (s, 9H; $SiC(CH_3)_3$), 1.55–1.66 (m, 4H; H-4, H-5), 2.49 (ddd, $J=15.8$, 5.5, 2.4 Hz, 1H; H-2a), 2.53 (ddd, $J=15.8$, 5.9, 2.6 Hz, 1H; H-2b), 3.43 (t, $J=5.8$ Hz, 2H; H-6), 3.79 (s, 3H; PMB CH_3), 4.16–4.24 (m, 1H; H-3), 4.41 (s, 2H; PMB CH_2), 6.86 (d, $J=8.6$ Hz, 2H; PMB H-3,5), 7.24 (d, $J=8.6$ Hz, 2H; PMB H-2,6), 9.79 ppm (dd, $J=2.6$, 2.4 Hz, 1H; H-1); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.7$ ($Si(CH_3)_2$), -4.5 ($Si(CH_3)_2$), 17.9 (SiC), 25.4 (C-5), 25.7 ($C(CH_3)_3$), 34.4 (C-4), 50.8 (C-2), 55.2 (PMB CH_3), 67.9 (C-3), 69.8 (C-6) 72.5 (PMB CH_2), 113.7 (PMB C-3,5), 129.2 (PMB C-2,6), 130.5 (PMB C-1), 159.1 (PMB C-4), 202.2 ppm (C-1); IR (film): $\tilde{\nu}=1006$, 1038, 1096, 1173, 1249, 1362, 1464, 1514, 1613, 1725, 2856, 2930, 2953 cm^{-1}; MS (EI): m/z (%): 190 (5), 189 (4), 187 (7), 171 (10), 152 (11), 145 (43), 135 (32), 122 (22), 121 (100), 77 (17), 75 (95), 73 (16), 71 (18); HRMS (EI): calcd for $C_{20}H_{34}NaO_4Si$ $[M+\mathrm{Na}]^+$: 389.21186; found: 389.21205.

(4*S*)-4-Benzyl-3-{(2*S*,3*R*,5*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-3-hydroxy-8-[(4-methoxybenzyl)oxy]-2-methyloctanoyl}-1,3-oxazolidin-2-one (10): Titanium(IV) chloride (0.94 mL, 1.62 g, 8.55 mmol) was added dropwise to a stirred, cooled (0 °C) solution of (4*S*)-4-(benzyl)-3-propanoyl-1,3-oxazolidin-2-one[23] (**9**) (1.90 g, 8.15 mmol) in CH_2Cl_2 (60 mL) and the resulting mixture was allowed to stir for 5 min. Subsequently, TMEDA (3.05 mL, 2.37 g, 20.4 mmol) was added to the yellow slurry. The dark-red enolate solution was stirred for 20 min at 0 °C before a solution of aldehyde **8** (3.28 g, 8.96 mmol) in CH_2Cl_2 (45 mL) was added dropwise and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with half-saturated aqueous NH_4Cl solution (20 mL) and allowed to warm to room temperature. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography afforded the desired product **10** (3.81 g, 78 %) as a colorless viscous oil. $R_f=0.48$ (petroleum ether/diethyl ether, 2:3); $[\alpha]_D=+35.4$ ($c=1.43$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.06$, 0.07 (2 × s, 3H each; $Si(CH_3)_2$), 0.86 (s, 9H; $SiC(CH_3)_3$), 1.25 (d, $J=7.0$ Hz, 3H; CH_3), 1.51–1.72 (m, 6H; H-6, H-4, H-7), 2.75 (dd, $J=13.4$, 9.6 Hz, 1H; Bn CH_2), 3.25 (dd, $J=13.4$, 3.2 Hz, 1H; Bn CH_2), 3.31 (br s, 1H; OH), 3.39–3.45 (m, 2H; H-8), 3.74 (qd, $J=7.0$, 4.0 Hz, 1H; H-2), 3.78 (s, 3H; PMB CH_3), 3.90–3.98 (m, 1H; H-5), 4.05 (ddd, $J=9.2$, 3.8, 3.0 Hz, 1H; H-3), 4.15 (dd, $J=9.1$, 3.3 Hz, 1H; H-5′a), 4.18 (dd, $J=9.1$, 6.8 Hz, 1H; H-5′b), 4.41 (s, 2H; PMB CH_2), 4.67 (dddd, $J=9.6$, 6.8, 3.3, 3.2 Hz, 1H; H-4′), 6.86 (d, $J=8.6$ Hz, 2H; PMB H-3,5), 7.18–7.34 ppm (m, 7H; Bn H, PMB H-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.7$ ($Si(CH_3)_2$), -4.2 ($Si(CH_3)_2$), 11.2 (CH_3), 18.0 (SiC), 25.0 (C-7), 25.8 ($C(CH_3)_3$), 33.9 (C-6), 37.7 (Bn CH_2), 40.4 (C-4), 42.8 (C-2), 55.2 (PMB CH_3), 55.3 (C-4′), 66.1 (C-5′), 70.1 (C-8), 70.3 (C-3), 71.6 (C-5), 72.5 (PMB CH_2), 113.7 (PMB C-3,5), 127.4 (Bn C-4), 128.9 (Bn C-3,5), 129.2 (PMB C-2,6), 129.4 (Bn C-2,6), 130.6 (PMB C-1), 135.2 (Bn C-1), 153.0 (C-2′), 159.1 (PMB C-4), 176.5 ppm (C-1); IR (film): $\tilde{\nu}=1037$, 1112, 1210, 1248, 1362, 1385, 1455, 1513, 1696, 1783, 2856, 2930, 2953, 3525 cm^{-1}; MS (EI): m/z (%): 233 (2), 142 (3), 122 (10), 121 (100), 91 (5), 57 (10); HRMS (ESI): calcd for $C_{33}H_{49}NNaO_7Si$ $[M+\mathrm{Na}]^+$: 622.31705; found: 622.31728.

(4*S*)-4-Benzyl-3-[(2*S*,3*R*,5*R*)-5-{[*tert*-butyl(dimethyl)silyl]oxy}-8-[(4-methoxybenzyl)oxy]-3-(methoxymethoxy)-2-methyloctanoyl]-1,3-oxazolidin-2-one (11): *N*,*N*-diisopropylethylamine (2.60 mL, 1.97 g, 15.2 mmol), chloromethylmethyl ether (0.58 mL, 0.61 g, 7.60 mmol), and TBAI

(28 mg, 76 µmol) were added to a stirred, cooled (0°C) solution of alcohol **10** (0.46 g, 0.76 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was protected from light and allowed to warm to room temperature within 12 h while being stirred. The reaction mixture was treated with saturated aqueous $NaHCO_3$ solution (20 mL) and diluted with Et_2O (30 mL). After separation of the phases, the organic layer was washed with 1 N HCl (10 mL) and brine (6 mL), and the aqueous layer was extracted with Et_2O (2×20 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography of the residue provided MOM ether **11** (0.42 g, 86%) as a slightly yellow viscous oil. $R_f=0.62$ (petroleum ether/diethyl ether, 1:2); $[\alpha]_D=+70.3$ ($c=1.22$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.02$, 0.03 (2×s, 3H each; $\mathrm{Si}(\mathrm{C}H_3)_2$), 0.86 (s, 9H; $\mathrm{SiC}(\mathrm{C}H_3)_3$), 1.21 (d, $J=7.0$ Hz, 3H; $\mathrm{C}H_3$), 1.39–1.48 (m, 1H; *H*-6a), 1.53–1.78 (m, 5H; *H*-7a, *H*-6b, *H*-7b, *H*-4), 2.75 (dd, $J=13.4$, 9.7 Hz, 1H; Bn $\mathrm{C}H_2$), 3.27 (dd, $J=13.4$, 3.0 Hz, 1H; Bn $\mathrm{C}H_2$), 3.30 (s, 3H; MOM $\mathrm{C}H_3$), 3.43 (t, $J=6.5$ Hz, 2H; *H*-8), 3.77 (s, 3H; PMB $\mathrm{C}H_3$), 3.79–3.85 (m, 2H; *H*-3, *H*-5), 3.96 (qd, $J=7.0$, 4.4 Hz, 1H; *H*-2), 4.09–4.17 (m, 2H; *H*-5′), 4.41 (s, 2H; PMB $\mathrm{C}H_2$), 4.54 (d, $J=7.1$ Hz, 1H; MOM $\mathrm{C}H_2$), 4.55–4.62 (m, 1H; *H*-4′), 4.60 (d, $J=7.1$ Hz, 1H; MOM $\mathrm{C}H_2$), 6.85 (d, $J=8.6$ Hz, 2H; PMB *H*-3,5), 7.17–7.33 ppm (m, 7H; Bn *H*-2,6, PMB *H*-2,6, Bn *H*-4, Bn *H*-3,5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.6$ ($\mathrm{Si}(C\mathrm{H}_3)_2$), −4.5 ($\mathrm{Si}(C\mathrm{H}_3)_2$), 12.1 ($C\mathrm{H}_3$), 18.0 (Si*C*), 25.3 (*C*-7), 25.9 ($\mathrm{C}(C\mathrm{H}_3)_3$), 32.7 (*C*-6), 37.7 (Bn $C\mathrm{H}_2$), 40.7 (*C*-4), 41.8 (*C*-2), 55.2 (PMB $C\mathrm{H}_3$), 55.8 (*C*-4′), 56.1 (MOM $C\mathrm{H}_3$) 66.0 (*C*-5′), 69.2 (*C*-5), 70.3 (*C*-8), 72.3 (PMB $C\mathrm{H}_2$), 76.6 (*C*-3), 96.5 (MOM $C\mathrm{H}_2$), 113.7 (PMB *C*-3,5), 127.3 (Bn *C*-4), 128.9 (Bn *C*-3,5), 129.2 (PMB *C*-2,6), 129.4 (Bn *C*-2,6), 130.8 (PMB *C*-1), 135.3 (Bn *C*-1), 153.2 (*C*-2′), 159.0 (PMB *C*-4), 174.8 ppm (*C*-1); IR (film): $\tilde{\nu}=1035$, 1100, 1210, 1249, 1382, 1455, 1513, 1782, 2855, 2930, 2953 cm^{-1}; MS (EI): *m*/*z* (%): 233 (8), 177 (4), 149 (11), 142 (16), 136 (36), 135 (56), 121 (68), 91 (22), 75 (36), 57 (100); HRMS (ESI): calcd for $C_{35}H_{53}NNaO_8Si$ $[M+Na]^+$: 666.34327; found: 666.34223.

(2*R*,3*R*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-8-[(4-methoxybenzyl)oxy]-3-(methoxymethoxy)-2-methyl-1-octanol (12): A solution of sodium borohydride (0.81 g, 21.5 mmol) in water (22 mL) was added dropwise to a cooled (0°C) solution of amide **11** (2.77, 4.30 mmol) in THF (45 mL). Stirring was continued for 12 h with concomitant warming of the mixture to room temperature. The solution was treated with saturated aqueous NH_4Cl solution (40 mL), stirred for 1 h, and transferred into a separation funnel. After extraction with ethyl acetate (3×40 mL), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue provided alcohol **12** (1.63 g, 80%) as a colorless oil. $R_f=0.42$ (petroleum ether/ethyl acetate, 2:1); $[\alpha]_D=-13.4$ ($c=1.20$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.03$, 0.05 (2×s, 3H each; $\mathrm{Si}(\mathrm{C}H_3)_2$), 0.80 (d, $J=7.0$ Hz, 3H; $\mathrm{C}H_3$), 0.87 (s, 9H; $\mathrm{SiC}(\mathrm{C}H_3)_3$), 1.43–1.75 (m, 6H; *H*-6, *H*-7, *H*-4), 1.88–1.98 (m, 1H; *H*-2), 2.70 (brs, 1H; O*H*), 3.37 (s, 3H; MOM $\mathrm{C}H_3$), 3.42 (t, $J=6.4$ Hz, 2H; *H*-8), 3.51 (dd, $J=11.0$, 5.3 Hz, 1H *H*-1a), 3.60 (dd, $J=11.0$, 8.9 Hz, 1H; *H*-1b), 3.71–3.77 (m, 1H; *H*-5), 3.77–3.84 (m, 1H; *H*-3), 3.79 (s, 3H; PMB $\mathrm{C}H_3$), 4.41 (s, 2H; PMB $\mathrm{C}H_2$), 4.60 (d, $J=6.6$ Hz, 1H; MOM $\mathrm{C}H_2$), 4.62 (d, $J=6.6$ Hz, 1H; MOM $\mathrm{C}H_2$), 6.86 (d, $J=8.6$ Hz, 2H; PMB *H*-3,5), 7.24 ppm (d, $J=8.6$ Hz, 2H; PMB *H*-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.4$ ($\mathrm{Si}(C\mathrm{H}_3)_2$), −4.4 ($\mathrm{Si}(C\mathrm{H}_3)_2$), 10.9 ($C\mathrm{H}_3$), 18.0 (Si*C*), 25.4 (*C*-7), 25.9 ($\mathrm{C}(C\mathrm{H}_3)_3$), 33.6 (*C*-6), 37.7 (*C*-2), 38.6 (*C*-4), 55.2 (PMB $C\mathrm{H}_3$), 55.9 (MOM $C\mathrm{H}_3$) 65.3 (*C*-1), 69.2 (*C*-5), 70.2 (*C*-8), 72.5 (PMB $C\mathrm{H}_2$), 76.7 (*C*-3), 96.3 (MOM $C\mathrm{H}_2$), 113.7 (PMB *C*-3,5), 129.2 (PMB *C*-2,6), 130.6 (PMB *C*-1), 159.1 ppm (PMB *C*-4); IR (film): $\tilde{\nu}=1038$, 1095, 1249, 1514, 2856, 2930, 2952, 3466 cm^{-1}; MS (EI): *m*/*z* (%): 349 (2), 167 (2), 149 (7), 122 (9), 121 (100), 89 (6), 77 (6), 73 (6), 59 (9), 58 (9), 43 (36); HRMS (ESI): calcd for $C_{25}H_{46}NaO_6Si$ $[M+Na]^+$: 493.29559; found: 493.29557.

(2*R*,3*R*,5*R*)-5-{[*tert*-Butyl(dimethyl)silyl]oxy}-8-[(4-methoxybenzyl)oxy]-3-(methoxymethoxy)-2-methyloctyl 4-methylbenzenesulfonate (13): *p*-Toluenesulfonyl chloride (1.17 g, 6.11 mmol) was added to a stirred solution of alcohol **12** (0.96 g, 2.04 mmol) in pyridine (4 mL) at 0°C. After being stirred for 5 h, the reaction was quenched by addition of ice (0.5 g) and H_2O (8 mL). The mixture was diluted with Et_2O (40 mL) and washed with saturated aqueous $NaHCO_3$ solution (7 mL), 1 N HCl (7 mL), and brine (7 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Filtration of the residue over a short pad of silica gel and evaporation of the solvent gave the pure tosylate **13** (1.27 g, 100%) as a colorless oil. $R_f=0.55$ (petroleum ether/diethyl ether, 1:1); $[\alpha]_D=+1.6$ ($c=1.00$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.01$, 0.01 (2×s, 3H each; $\mathrm{Si}(\mathrm{C}H_3)_2$), 0.82–0.87 (m, 3H; $\mathrm{C}H_3$), 0.84 (s, 9H; $\mathrm{SiC}(\mathrm{C}H_3)_3$), 1.40–1.65 (m, 6H; *H*-6, *H*-7, *H*-4), 1.98–2.09 (m, 1H; *H*-2), 2.43 (s, 3H; Ts $\mathrm{C}H_3$), 3.25 (s, 3H; MOM $\mathrm{C}H_3$), 3.40 (t, $J=6.5$ Hz, 2H; *H*-8), 3.63 (td, $J=6.5$, 2.6 Hz, 1H; *H*-3), 3.65–3.72 (m, 1H; *H*-5), 3.79 (s, 3H; PMB $\mathrm{C}H_3$), 3.87 (dd, $J=9.2$, 7.5 Hz, 1H; *H*-1a), 4.05 (dd, $J=9.2$, 6.4 Hz, 1H; *H*-1b), 4.41 (s, 2H; PMB $\mathrm{C}H_2$), 4.45 (d, $J=6.8$ Hz, 1H; MOM $\mathrm{C}H_2$), 4.50 (d, $J=6.8$ Hz, 1H; MOM $\mathrm{C}H_2$), 6.86 (d, $J=8.6$ Hz, 2H; PMB *H*-3,5), 7.24 (d, $J=8.6$ Hz, 2H; PMB *H*-2,6), 7.32 (d, $J=8.2$ Hz, 2H; Ts *H*-3,5), 7.77 ppm (d, $J=8.2$ Hz, 2H; Ts *H*-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.5$ ($\mathrm{Si}(C\mathrm{H}_3)_2$), −4.4 ($\mathrm{Si}(C\mathrm{H}_3)_2$), 10.8 ($C\mathrm{H}_3$), 18.0 (Si*C*), 21.6 (Ts $C\mathrm{H}_3$), 25.3 (*C*-7), 25.8 ($\mathrm{C}(C\mathrm{H}_3)_3$), 33.5 (*C*-6), 36.0 (*C*-2), 38.5 (*C*-4), 55.2 (PMB $C\mathrm{H}_3$), 55.7 (MOM $C\mathrm{H}_3$) 69.0 (*C*-5), 70.1 (*C*-8), 72.4 (*C*-1), 72.5 (PMB $C\mathrm{H}_2$), 75.1 (*C*-3), 96.2 (MOM $C\mathrm{H}_2$), 113.7 (PMB *C*-3,5), 127.9 (Ts *C*-2,6), 129.2 (PMB *C*-2,6), 129.8 (Ts *C*-3,5), 130.6 (PMB *C*-1), 133.1 (Ts *C*-1), 144.6 (Ts *C*-4), 159.1 ppm (PMB *C*-4); IR (film): $\tilde{\nu}=969$, 1038, 1097, 1178, 1189, 1249, 1363, 1464, 1513, 2855, 2929, 2952 cm^{-1}; MS (EI): *m*/*z* (%): 233 (2), 189 (6), 147 (34), 122 (10), 121 (100), 91 (6), 57 (17); HRMS (ESI): calcd for $C_{32}H_{52}NaO_8SSi$ $[M+Na]^+$: 647.30444; found: 647.30360.

(4*R*,6*R*)-4-{[tert-Butyl(dimethyl)silyl]oxy}-1-[(4-methoxybenzyl)oxy]-6-(methoxymethoxy)-7-methyloct-7-ene (14): A mixture of tosylate **13** (1.54 g, 2.46 mmol), NaI (923 mg, 6.16 mmol), and DBU (1.86 mL, 1.88 g, 12.3 mmol) in glyme (35 mL) was refluxed with stirring for 3 h. The solution was cooled to room temperature, diluted with Et_2O (60 mL), and washed with saturated aqueous $NaHCO_3$ solution (10 mL), 1 N HCl (10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Filtration of the residue over a short pad of silica gel gave pure alkene **14** (0.99 g, 89%) as a slightly yellow oil. $R_f=0.78$ (petroleum ether/diethyl ether, 1:1); $[\alpha]_D=+53.4$ ($c=1.23$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.03$ (s, 6H; $\mathrm{Si}(\mathrm{C}H_3)_2$), 0.87 (s, 9H; $\mathrm{SiC}(\mathrm{C}H_3)_3$), 1.43–1.54 (m, 1H; *H*-3a), 1.55–1.73 (m, 4H; *H*-3b, *H*-5a, *H*-2), 1.63 (s, 3H; $\mathrm{C}H_3$), 1.74–1.84 (m, 1H; *H*-5b), 3.32 (s, 3H; MOM $\mathrm{C}H_3$), 3.42 (t, $J=6.4$ Hz, 2H; *H*-8), 3.74–3.80 (m, 1H; *H*-4), 3.78 (s, 3H; PMB $\mathrm{C}H_3$), 4.10 (dd, $J=7.7$, 5.9 Hz, 1H; *H*-6), 4.41 (s, 2H; PMB $\mathrm{C}H_2$), 4.44 (d, $J=6.7$ Hz, 1H; MOM $\mathrm{C}H_2$), 4.57 (d, $J=6.7$ Hz, 1H; MOM $\mathrm{C}H_2$), 4.91 (s, 2H; *H*-8), 6.85 (d, $J=8.6$ Hz, 2H; PMB *H*-3,5), 7.24 ppm (d, $J=8.6$ Hz, 2H; PMB *H*-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.4$ ($\mathrm{Si}(C\mathrm{H}_3)_2$), −4.3 ($\mathrm{Si}(C\mathrm{H}_3)_2$), 16.7 ($C\mathrm{H}_3$), 18.0 (Si*C*), 25.4 (*C*-2), 25.9 ($\mathrm{C}(C\mathrm{H}_3)_3$), 33.2 (*C*-3), 41.2 (*C*-5), 55.2 (PMB $C\mathrm{H}_3$), 55.5 (MOM $C\mathrm{H}_3$) 69.2 (*C*-4), 70.3 (*C*-1), 72.4 (PMB $C\mathrm{H}_2$), 76.9 (*C*-6), 93.3 (MOM $C\mathrm{H}_2$), 113.7 (PMB *C*-3,5), 114.2, (*C*-8), 129.1 (PMB *C*-2,6), 130.7 (PMB *C*-1), 143.8 (*C*-7), 159.0 ppm (PMB *C*-4); IR (film): $\tilde{\nu}=1037$, 1065, 1095, 1153, 1249, 1463, 1514, 1613, 2856, 2886, 2930, 2952 cm^{-1}; MS (EI): *m*/*z* (%): 292 (3), 149 (4), 135 (7), 122 (9), 121 (100), 89 (8), 77 (10), 57 (7); HRMS (ESI): calcd for $C_{25}H_{44}NaO_5Si$ $[M+Na]^+$: 475.28502; found: 475.28523.

Methyl 2-[(2*E*,5*S*,6*R*,8*R*)-8-{[*tert*-butyl(dimethyl)silyl]oxy}-11-[(4-methoxybenzyl)oxy]-6-(methoxymethoxy)-5-methyl-2-undecenyl]-6-methoxybenzoate (16): 9-BBN (0.5 M solution in THF, 2.67 mL, 1.34 mmol) was added to olefin **14** (403 mg, 0.89 mmol) in THF (9 mL) at 0°C. After being stirred for 12 h at room temperature, the solution was cooled to 0°C and treated with $[PdCl_2(dppf)]$ (73 mg, 0.089 mmol), vinyl iodide[15e] **15** (266 mg, 0.80 mmol), and 3 N NaOH (0.89 mL). The mixture was heated to 40°C for 4 h, cooled to room temperature, and diluted with Et_2O (20 mL) and brine (20 mL). After separation of the phases, the aqueous layer was extracted with Et_2O (3×20 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/ethyl acetate, 4:1, and CH_2Cl_2/acetone, 30:1) afforded coupling product **16** (444 mg, 84%) as a light-yellow oil. $R_f=0.29$ (petroleum ether/ethyl acetate, 5:1); $[\alpha]_D=+15.5$ ($c=1.38$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.04$, 0.05 (2×s, 3H each; $\mathrm{Si}(\mathrm{C}H_3)_2$), 0.85–0.90 (m, 3H; $\mathrm{C}H_3$), 0.88 (s, 9H; $\mathrm{SiC}(\mathrm{C}H_3)_3$), 1.34–1.52 (m, 2H; *H*-9a, *H*-7a), 1.52–1.75 (m, 4H; *H*-9b, *H*-7b, *H*-10), 1.75–1.85 (m, 2H; *H*-5, *H*-4a), 2.00–2.05 (m, 1H; *H*-4b), 3.27 (d, $J=6.1$ Hz, 2H; *H*-1), 3.34 (s, 3H; MOM $\mathrm{C}H_3$), 3.41 (t, $J=6.5$ Hz, 2H; *H*-11), 3.43–3.49 (m, 1H; *H*-6), 3.77 (s, 3H; PMB $\mathrm{C}H_3$), 3.79 (s, 3H; Ph–$\mathrm{OC}H_3$), 3.79–3.85 (m, 1H; *H*-8), 3.87 (s, 3H; $\mathrm{CO_2C}H_3$), 4.41 (s, 2H; PMB $\mathrm{C}H_2$), 4.55 (d, $J=6.8$ Hz, 1H; MOM $\mathrm{C}H_2$), 4.60 (d, $J=6.8$ Hz, 1H; MOM $\mathrm{C}H_2$), 5.41 (dt, $J=15.2$, 6.4 Hz, 1H; *H*-3), 5.51 (dt, $J=15.2$, 6.1 Hz, 1H; *H*-2), 6.75 (d, $J=8.3$ Hz, 1H; *H*-3′), 6.80 (d, $J=7.6$ Hz, 1H; *H*-5′), 6.85 (d, $J=8.5$ Hz, 2H; PMB *H*-3,5), 7.24 (d, $J=8.5$ Hz, 2H; PMB *H*-2,6), 7.24–7.27 ppm (m, 1H; *H*-4′); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=-4.6$

($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 14.1 (CH_3), 18.0 (Si*C*), 25.3 (*C*-10), 25.8 ($C(CH_3)_3$), 32.8 (*C*-9), 35.6 (*C*-4), 36.1 (*C*-1), 36.4 (*C*-5), 37.7 (*C*-7), 52.0 (CO_2CH_3), 55.1 (PMB CH_3), 55.6 (MOM CH_3) 55.7 (Ph−OCH_3), 69.4 (*C*-8), 70.2 (*C*-11), 72.3 (PMB CH_2), 78.3 (*C*-6), 95.6 (MOM CH_2), 108.6 (*C*-3′), 113.6 (PMB *C*-3,5), 121.5 (*C*-5′), 123.3 (*C*-1′), 129.1 (PMB *C*-2,6), 129.1 (*C*-2), 130.3 (*C*-4′), 130.6 (PMB *C*-1), 130.7 (*C*-3), 139.2 (*C*-6′), 156.3 (*C*-2′), 159.0 (PMB *C*-4), 168.5 ppm (CO_2CH_3); IR (film): $\tilde{\nu}=1038$, 1071, 1109, 1249, 1470, 1513, 1734, 2855, 2931, 2952 cm^{-1}; MS (EI): *m*/*z* (%): 293 (2), 192 (5), 181 (10), 178 (10), 176 (10), 170 (17), 168 (12), 166 (16), 150 (16), 141 (17), 137 (47), 121 (100), 97 (14), 77 (8); HRMS (ESI): calcd for $C_{37}H_{58}NaO_8Si$ [*M*+Na]$^+$: 681.37932; found: 681.37870.

Methyl 2-[(2*E*,5*S*,6*R*,8*R*)-8-hydroxy-11-[(4-methoxybenzyl)oxy]-6-(methoxymethoxy)-5-methyl-2-undecenyl]-6-methoxybenzoate (17): TBAF (1 M in THF, 1.57 mL, 1.57 mmol) was added to a solution of TBDMS ether **16** (345 mg, 0.52 mmol) in THF (5.2 mL) at 0 °C. After being stirred for 2 days, the solution was treated with saturated aqueous $NaHCO_3$ solution (10 mL) and the mixture was extracted with Et_2O (3 × 15 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated. Flash chromatography of the residue gave the desired alcohol **17** (284 mg, 100 %) as a colorless oil. $R_f=0.53$ (diethyl ether); $[\alpha]_D=+19.5$ ($c=1.00$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.85$ (d, $J=6.3$ Hz, 3 H; CH_3), 1.40–1.60 (m, 4 H; *H*-7, *H*-9), 1.60–1.75 (m, 2 H; *H*-10), 1.75–2.00 (m, 4 H; *H*-4a, *H*-5, *H*-4b), 3.27 (d, $J=6.4$ Hz, 2 H; *H*-1), 3.37 (s, 3 H; MOM CH_3), 3.42–3.48 (m, 2 H; *H*-11), 3.53 (d, $J=1.7$ Hz, 1 H; O*H*), 3.65–3.74 (m, 2 H; *H*-6, *H*-8), 3.77 (s, 3 H; PMB CH_3), 3.79 (s, 3 H; Ph−OCH_3), 3.87 (s, 3 H; CO_2CH_3), 4.42 (s, 2 H; PMB CH_2), 4.60 (d, $J=6.8$ Hz, 1 H; MOM CH_2), 4.69 (d, $J=6.8$ Hz, 1 H; MOM CH_2), 5.39 (dt, $J=15.2$, 6.5 Hz, 1 H; *H*-3), 5.50 (dt, $J=15.2$, 6.4 Hz, 1 H; *H*-2), 6.75 (d, $J=8.4$ Hz, 1 H; *H*-3′), 6.79 (d, $J=7.7$ Hz, 1 H; *H*-5′), 6.85 (d, $J=8.6$ Hz, 2 H; PMB *H*-3,5), 7.24 (d, $J=8.6$ Hz, 2 H; PMB *H*-2,6), 7.26 ppm (dd, $J=8.4$, 7.7 Hz, 1 H; *H*-4′); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.5$ (CH_3), 25.7 (*C*-10), 34.3 (*C*-9), 35.5 (*C*-5), 35.9 (*C*-7), 36.0 (*C*-4), 36.3 (*C*-1), 52.0 (CO_2CH_3), 55.1 (PMB CH_3), 55.7 (Ph−OCH_3), 55.8 (MOM CH_3), 70.0 (*C*-11), 70.8 (*C*-8), 72.4 (PMB CH_2), 81.0 (*C*-6), 95.3 (MOM CH_2), 108.7 (*C*-3′), 113.6 (PMB *C*-3,5), 121.4 (*C*-5′), 123.2 (*C*-1′), 129.1 (PMB *C*-2,6), 129.4 (*C*-2), 130.2 (*C*-3), 130.3 (*C*-4′), 130.4 (PMB *C*-1), 139.1 (*C*-6′), 156.3 (*C*-2′), 159.0 (PMB *C*-4), 168.5 ppm (CO_2CH_3); IR (film): $\tilde{\nu}=1169$, 1248, 1263, 1363, 1439, 1469, 1513, 1584, 1732, 2849, 2948, 3494 cm^{-1}; MS (EI): *m*/*z* (%): 359 (2), 311 (3), 243 (3), 199 (4), 190 (5), 187 (7), 137 (11), 122 (10), 121 (100); HRMS (ESI): calcd for $C_{31}H_{44}NaO_8$ [*M*+Na]$^+$: 567.29284; found: 567.29316.

2-[(2*E*,5*S*,6*R*,8*R*)-8-Hydroxy-11-[(4-methoxybenzyl)oxy]-6-(methoxymethoxy)-5-methyl-2-undecenyl]-6-methoxybenzoic acid (18): A solution of methyl ester **17** (352 mg, 0.65 mmol) in a mixture of THF (4 mL), ethanol (8 mL), and H_2O (8 mL) was treated with $LiOH\cdot H_2O$ (271 mg, 6.46 mmol) and stirred at 70 °C for 3 days. After being allowed to cool to room temperature, the reaction mixture was diluted with Et_2O (20 mL) and water (50 mL). The organic layer containing unreacted starting material and side products was washed with water (10 mL), dried (Na_2SO_4), and concentrated separately. The combined aqueous layers were acidified (pH ≈ 3) by addition of 1 N HCl at 0 °C and extracted with EtOAc (3 × 30 mL). The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), filtered, and concentrated to give the desired acid **18** (317 mg, 92 %) as a light-yellow oil. $R_f=0.52$ (petroleum ether/ethyl acetate, 1:3); $[\alpha]_D=+26.5$ ($c=0.75$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.84$ (d, $J=6.3$ Hz, 3 H; CH_3), 1.42–1.62 (m, 4 H; *H*-9, *H*-7), 1.62–1.75 (m, 2 H; *H*-10), 1.78–1.99 (m, 4 H; *H*-4a, *H*-5, *H*-4b), 3.31–3.57 (m, 2 H; *H*-1), 3.41 (s, 3 H; MOM CH_3), 3.43–3.57 (m, 1 H; O*H*), 3.45 (t, $J=6.6$ Hz, 2 H; *H*-11), 3.67–3.83 (m, 2 H; *H*-8, *H*-6), 3.77 (s, 3 H; PMB CH_3), 3.81 (s, 3 H; Ph−OCH_3), 4.44 (s, 2 H; PMB CH_2), 4.61 (d, $J=6.9$ Hz, 1 H; MOM CH_2), 4.77 (d, $J=6.9$ Hz, 1 H; MOM CH_2), 5.36–5.54 (m, 2 H; *H*-3, *H*-2), 6.77 (d, $J=8.3$ Hz, 1 H; *H*-3′), 6.78 (d, $J=7.4$ Hz, 1 H; *H*-5′), 6.85 (d, $J=8.5$ Hz, 2 H; PMB *H*-3,5), 6.97 (brs, 1 H; CO_2H), 7.24 (d, $J=8.5$ Hz, 2 H; PMB *H*-2,6), 7.24–7.28 ppm (m, 1 H; *H*-4′); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.8$ (CH_3), 25.7 (*C*-10), 34.0 (*C*-9), 35.0 (*C*-7), 35.0 (*C*-5), 36.4 (*C*-4), 36.9 (*C*-1), 55.2 (PMB CH_3), 55.7 (MOM CH_3), 55.9 (Ph−OCH_3), 70.0 (*C*-11), 71.1 (*C*-8), 72.4 (PMB CH_2), 79.4 (*C*-6), 94.4 (MOM CH_2), 109.1 (*C*-3′), 113.7 (PMB *C*-3,5), 122.2 (*C*-5′), 122.9 (*C*-1′), 129.4 (PMB *C*-2,6), 129.6 (*C*-2), 129.8 (*C*-3), 130.2 (PMB *C*-1), 130.6 (*C*-4′), 139.6 (*C*-6′), 156.6 (*C*-2′), 159.1 (PMB *C*-4), 169.5 ppm (CO_2H); IR (film): $\tilde{\nu}=1035$, 1083, 1249, 1265, 1470, 1513, 1584, 1725, 2840, 2937, 3431 cm^{-1}; MS (EI): *m*/*z* (%): 361(2), 311 (2), 187 (5), 137 (12), 122 (13), 121 (100); HRMS (ESI): calcd for $C_{30}H_{42}NaO_8$ [*M*+Na]$^+$: 553.27719; found: 553.27712.

(3*S*,5*R*,6*S*)-14-Methoxy-3-{3-[(4-methoxybenzyl)oxy]propyl}-5-(methoxymethoxy)-6-methyl-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (19)

*Method A (from the hydroxy acid **18**)*: Polymer-bound PPh_3 (1.6 mmol of P per g of resin, 365 mg, 584 μmol) was added to a cooled (0 °C) solution of hydroxy acid **18** (62 mg, 117 μmol) in THF (5.9 mL). After being shaken for 15 min at room temperature, the slurry was recooled to 0 °C and treated dropwise with DEAD (≈40 % solution in toluene, 102 μL, 41 mg, 234 μmol). Over a period of 24 h with agitation, the reaction mixture was allowed to warm to room temperature. The resin was filtered off and washed thoroughly with THF. After evaporation of the solvent, the residue was purified by flash chromatography to give the desired lactone (*E*)-**19** (43 mg, 72 %) as a colorless oil. $R_f=0.75$ (petroleum ether/ethyl acetate, 1:1).

*Method B (by ring-closing metathesis from the diene **28**)*: The second-generation Grubbs catalyst **29** (13.3 mg, 15.7 μmol) was added to a solution of diene **28** (85.0 mg, 157 μmol) in toluene (160 mL) and the light-purple solution was heated to 70 °C for 2 h. After completion of the reaction (checked by ^{1}H NMR spectroscopy), ethoxyethylene (0.41 mL, 567 mg, 7.86 mmol) was added and the solution was allowed to cool to room temperature. The solvent was removed in vacuo and the residue was purified by flash chromatography. Both isomers, *E* macrolactone (*E*)-**19** (61.0 mg, 75 %) and *Z* derivative (*Z*)-**19** (9.8 mg, 12 %), could be isolated as slightly yellow waxes.

*Compound (E)-**19***: $[\alpha]_D=-42.3$ ($c=1.25$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.85$ (d, $J=6.8$ Hz, 3 H; CH_3), 1.41 (dd, $J=15.5$, 9.4 Hz, 1 H; *H*-14a), 1.62–1.78 (m, 5 H; *H*-11a, *H*-16, *H*-14b, *H*-17a), 1.82–1.90 (m, 1 H; *H*-17b), 2.06–2.16 (m, 1 H; *H*-12), 2.28 (brd, $J=14.2$ Hz, 1 H; *H*-11b), 3.31 (brd, $J=16.6$ Hz, 1 H; *H*-8a), 3.43 (s, 3 H; MOM CH_3), 3.47 (t, $J=6.3$ Hz, 2 H; *H*-18), 3.70 (dd, $J=16.6$, 9.5 Hz, 1 H; *H*-8b), 3.74 (s, 3 H; PMB CH_3), 3.79 (s, 3 H; Ph−OCH_3), 4.10–4.15 (m, 1 H; *H*-13), 4.42 (s, 2 H; PMB CH_2), 4.78 (d, $J=6.7$ Hz, 1 H; MOM CH_2), 4.89 (d, $J=6.7$ Hz, 1 H; MOM CH_2), 5.26–5.38 (m, 2 H; *H*-15, *H*-9), 5.42–5.52 (m, 1 H; *H*-10), 6.74 (d, $J=7.7$ Hz, 1 H; *H*-6), 6.78 (d, $J=8.4$ Hz, 1 H; *H*-4), 6.86 (d, $J=8.6$ Hz, 2 H; PMB *H*-3,5), 7.24 (d, $J=8.6$ Hz, 2 H; PMB *H*-2,6), 7.18–7.23 ppm (m, 1 H; *H*-5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.3$ (CH_3), 25.6 (*C*-17), 32.8 (*C*-16), 34.1 (*C*-12), 35.7 (*C*-14), 37.7 (*C*-8), 37.8 (*C*-11), 55.3 (PMB CH_3), 55.3 (Ph−OCH_3), 55.5 (MOM CH_3), 69.7 (*C*-18), 72.5 (PMB CH_2), 74.5 (*C*-15), 79.4 (*C*-13), 97.0 (MOM CH_2), 109.1 (*C*-4), 113.7 (PMB *C*-3,5), 122.7 (*C*-6), 124.7 (*C*-2), 128.6 (*C*-9), 129.1 (PMB *C*-2,6), 129.9 (*C*-5), 130.8 (PMB *C*-1), 131.3 (*C*-10), 138.9 (*C*-7), 156.5 (*C*-3), 159.1 (PMB *C*-4), 168.5 ppm (*C*-1); IR (film): $\tilde{\nu}=1040$, 1096, 1249, 1275, 1468, 1513, 1583, 1721, 2851, 2927, 2952 cm^{-1}; MS (EI): *m*/*z* (%): 480 (12), 467 (9), 315 (10), 259 (4), 245 (6), 227 (7), 203 (11), 190 (20), 134 (12), 122 (17), 121 (100), 45 (23); HRMS (ESI): calcd for $C_{30}H_{40}NaO_7$ [*M*+Na]$^+$: 535.26662; found: 535.26633.

*Compound (Z)-**19** (minor product from ring-closing metathesis)*: $R_f=0.48$ (petroleum ether/ethyl acetate, 2:1); $[\alpha]_D=-4.8$ ($c=1.00$, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=0.92$ (d, $J=6.2$ Hz, 3 H; CH_3), 1.56 (dd, $J=15.4$, 9.3 Hz, 1 H; *H*-14a), 1.65–1.80 (m, 4 H; *H*-17, *H*-16), 1.83–1.90 (m, 1 H; *H*-11a), 1.87 (dd, $J=15.4$, 9.7 Hz, 1 H; *H*-14b), 2.02–2.16 (m, 2 H; *H*-12, *H*-11b), 3.01 (brd, $J=15.6$ Hz, 1 H; *H*-8a), 3.39 (s, 3 H; MOM CH_3), 3.41–3.48 (m, 2 H; *H*-18), 3.77–3.81 (m, 1 H; *H*-13), 3.79 (s, 3 H; PMB CH_3), 3.80 (s, 3 H; Ph−OCH_3), 3.96 (br dd, $J=15.6$, 8.4 Hz, 1 H; *H*-8b), 4.39 (s, 2 H; PMB CH_2), 4.72 (d, $J=6.7$ Hz, 1 H; MOM CH_2), 4.78 (d, $J=6.7$ Hz, 1 H; MOM CH_2), 5.30–5.40 (m, 3 H; *H*-9, *H*-10, *H*-15), 6.80 (d, $J=7.5$ Hz, 1 H; *H*-4), 6.80 (d, $J=8.5$ Hz, 1 H; *H*-6), 6.85 (d, $J=8.6$ Hz, 2 H; PMB *H*-3,5), 7.22 (d, $J=8.6$ Hz, 2 H; PMB *H*-2,6), 7.27 ppm (dd, $J=8.5$, 7.5 Hz, 1 H; *H*-5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.4$ (CH_3), 25.7 (*C*-17), 32.0 (*C*-11), 32.1 (*C*-16), 32.5 (*C*-8), 36.3 (*C*-14), 36.5 (*C*-12), 55.2 (PMB CH_3), 55.5 (MOM CH_3), 55.9 (Ph−OCH_3), 69.5 (*C*-18), 72.4 (PMB CH_2), 74.1 (*C*-15), 78.0 (*C*-13), 97.4 (MOM CH_2), 109.4 (*C*-4), 113.7 (PMB *C*-3,5), 122.7 (*C*-6), 123.6 (*C*-2), 128.7 (*C*-9), 129.2 (PMB *C*-2,6), 129.3 (*C*-10), 130.7 (PMB *C*-1), 130.7 (*C*-5), 140.0 (*C*-7), 157.1 (*C*-3), 159.1 (PMB *C*-4), 167.1 ppm (*C*-1); IR (film): $\tilde{\nu}=1038$, 1096, 1264, 1469, 1513, 1729, 2852, 2929, 2953, 3002 cm^{-1}; MS (EI): *m*/*z* (%): 480 (3), 467 (3), 331 (3), 314 (4), 227 (5), 203 (9), 190 (12), 163 (11), 148 (10), 122

(11), 121 (100), 91 (5), 45 (6); HRMS (FAB): calcd for $C_{30}H_{40}NaO_7$ $[M+Na]^+$: 535.26716; found: 535.27231.

(4*S*)-4-Benzyl-3-((2*S*)-2-{(1*R*,3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-hydroxy-6-[(4-methoxybenzyl)oxy]hexyl}-4-pentenoyl)-1,3-oxazolidin-2-one (21): Titanium(IV) chloride (0.89 mL, 1.53 g, 8.07 mmol) was added dropwise to a stirred, cooled (0 °C) solution of (4*S*)-4-benzyl-3-(4-pentenoyl)-1,3-oxazolidin-2-one[27] (**20**) (1.99 g, 7.69 mmol) in CH_2Cl_2 (80 mL) and the mixture was allowed to stir for 5 min. Subsequently, (−)-sparteine (4.42 mL, 4.51 g, 19.2 mmol) was added to the yellow slurry. The dark-red enolate solution was stirred for 20 min at 0 °C before a solution of aldehyde **8** (3.10 g, 8.46 mmol) in CH_2Cl_2 (45 mL) was added dropwise and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with half-saturated aqueous NH_4Cl solution (20 mL) and allowed to warm to room temperature. After separation of the layers, the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography afforded the desired product **21** (3.17 g, 68 %) as a colorless viscous oil. $R_f = 0.60$ (petroleum ether/diethyl ether, 2:3); $[\alpha]_D = +29.9$ ($c = 1.00$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.06, 0.08 (2 × s, 3H each; Si(CH_3)$_2$), 0.87 (s, 9H; SiC(CH_3)$_3$), 1.51–1.71 (m, 6H; *H*-4″, *H*-5″, *H*-2″), 2.40–2.50 (m, 1H; *H*-3′a), 2.56–2.65 (m, 2H; *H*-3′b, Bn C*H*$_2$), 3.23–3.32 (m, 2H; Bn C*H*$_2$, O*H*), 3.36–3.48 (m, 2H; *H*-6″), 3.78 (s, 3H; PMB C*H*$_3$), 3.91–3.98 (m, 1H; *H*-3″), 4.00–4.06 (m, 1H; *H*-1″), 4.06–4.16 (m, 3H; *H*-2′, *H*-5), 4.41 (s, 2H; PMB C*H*$_2$), 4.66 (dddd, *J* = 10.1, 5.6, 3.3, 3.3 Hz, 1H; *H*-4), 5.02 (brd, *J* = 10.1 Hz, 1H; *H*-5′a), 5.09 (brd, *J* = 17.1 Hz, 1H; *H*-5′b), 5.85 (dddd, *J* = 17.1, 10.1, 7.2, 7.2 Hz, 1H; *H*-4′), 6.86 (d, *J* = 8.6 Hz, 2H; PMB *H*-3,5), 7.17–7.33 ppm (m, 7H; Bn *H*-2,6, PMB *H*-2,6, Bn *H*-4, Bn *H*-3,5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.7$ (Si(CH_3)$_2$), −4.2 (Si(CH_3)$_2$), 17.9 (Si*C*), 24.9 (*C*-5″), 25.8 (C(CH_3)$_3$), 32.0 (*C*-3′), 34.1 (*C*-4″), 38.0 (Bn CH$_2$), 40.3 (*C*-2″), 47.6 (*C*-2′), 55.3 (PMB CH$_3$), 55.6 (*C*-4), 65.9 (*C*-5), 70.1 (*C*-6″), 70.7 (*C*-1″), 72.2 (*C*-3″), 72.5 (PMB CH$_2$), 113.7 (PMB *C*-3,5), 117.2 (*C*-5′), 127.3 (Bn *C*-4), 128.9 (Bn *C*-3,5), 129.2 (PMB *C*-2,6), 129.4 (Bn *C*-2,6), 130.6 (PMB *C*-1), 135.3 (Bn *C*-1), 135.4 (*C*-4′), 153.3 (*C*-2), 159.1 (PMB *C*-4), 174.6 ppm (*C*-1′); IR (film): $\tilde{\nu} = 1036$, 1100, 1207, 1250, 1386, 1513, 1612, 1697, 1781, 2856, 2929, 2953, 3482 cm^{-1}; MS (EI): *m/z* (%): 259 (6), 135 (7), 122 (17), 121 (100), 83 (18), 55 (8); HRMS (ESI): calcd for $C_{35}H_{51}NNaO_7Si$ $[M+Na]^+$: 648.33270; found: 648.33237.

(4*S*)-4-Benzyl-3-{(2*S*)-2-[(1*R*,3*R*)-3-{[*tert*-butyl(dimethyl)silyl]oxy}-6-[(4-methoxybenzyl)oxy]-1-(methoxymethoxy)hexyl]-4-pentenoyl}-1,3-oxazolidin-2-one (22): *N*,*N*-diisopropylethylamine (9.63 mL, 7.27 g, 56.2 mmol), chloromethylmethyl ether (2.14 mL, 2.26 g, 28.1 mmol), and TBAI (104 mg, 281 µmol) were added to a stirred, cooled (0 °C) solution of alcohol **21** (1.76 g, 2.81 mmol) in CH_2Cl_2 (28 mL). The reaction mixture was protected from light and stirred for 3 days at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (60 mL) and the mixture was diluted with Et_2O (100 mL). After separation of the phases, the organic layer was washed with 1 N HCl (30 mL) and brine (20 mL), then the aqueous layer was extracted with Et_2O (2 × 50 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography of the residue provided MOM ether **22** (1.54 g, 82 %) as a slightly yellow viscous oil. $R_f = 0.52$ (petroleum ether/ethyl acetate, 3:1); $[\alpha]_D = +72.3$ ($c = 1.50$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$, 0.04 (2 × s, 3H each; Si(CH_3)$_2$), 0.87 (s, 9H; SiC(CH_3)$_3$), 1.37–1.48 (m, 1H; *H*-4″a), 1.55–1.67 (m, 2H; *H*-4″b, *H*-5″a), 1.67–1.82 (m, 3H; *H*-5″b, *H*-2″), 2.32 (ddd, *J* = 14.1, 5.3, 5.3 Hz, 1H; *H*-3′a), 2.57 (ddd, *J* = 14.1, 8.7, 8.7 Hz, 1H; *H*-3′b), 2.67 (dd, *J* = 13.3, 10.0 Hz, 1H; Bn C*H*$_2$), 3.27 (dd, *J* = 13.3, 2.8 Hz, 1H; Bn C*H*$_2$), 3.33 (s, 3H; MOM C*H*$_3$), 3.43 (t, *J* = 6.4 Hz, 2H; *H*-6″), 3.77 (s, 3H; PMB C*H*$_3$), 3.76–3.88 (m, 2H; *H*-3″, *H*-1″), 4.08–4.15 (m, 2H; *H*-5), 4.42 (ddd, *J* = 14.3, 9.5, 4.6 Hz, 1H; *H*-2′), 4.42 (s, 2H; PMB C*H*$_2$), 4.50 (d, *J* = 7.1 Hz, 1H; MOM C*H*$_2$), 4.59–4.68 (m, 1H; *H*-4), 4.65 (d, *J* = 7.1 Hz, 1H; MOM C*H*$_2$), 5.03 (brd, *J* = 10.2 Hz, 1H; *H*-5′a), 5.10 (brd, *J* = 17.1 Hz, 1H; *H*-5′b), 5.81 (dddd, *J* = 17.1, 10.2, 6.9, 6.9 Hz, 1H; *H*-4′), 6.86 (d, *J* = 8.6 Hz, 2H; PMB *H*-3,5), 7.18–7.34 ppm (m, 7H; Bn *H*-2,6, PMB *H*-2,6, Bn *H*-4, Bn *H*-3,5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.7$ (Si(CH_3)$_2$), −4.4 (Si(CH_3)$_2$), 18.0 (Si*C*), 25.3 (*C*-5″), 25.9 (C(CH_3)$_3$), 32.4 (*C*-4″), 32.6 (*C*-3′), 37.8 (Bn CH$_2$), 40.2 (*C*-2″), 45.7 (*C*-2′), 55.2 (PMB CH$_3$), 55.9 (*C*-4), 56.1 (MOM CH$_3$), 65.7 (*C*-5), 69.1 (*C*-1″), 70.2 (*C*-6″), 72.3 (PMB CH$_2$), 75.9 (*C*-3″), 96.1 (MOM CH$_2$), 113.6 (PMB *C*-3,5), 117.1 (*C*-5′), 127.2 (Bn *C*-4), 128.8 (Bn *C*-3,5), 129.1 (PMB *C*-2,6), 129.4 (Bn *C*-2,6), 130.7 (PMB *C*-1), 135.1 (*C*-4′), 135.4 (Bn *C*-1), 153.2 (*C*-2), 159.0 (PMB *C*-4), 173.4 ppm (*C*-1′); IR (film): $\tilde{\nu} = 1031$, 1099, 1249, 1383, 1513, 1612, 1698, 1781, 2855, 2929, 2955 cm^{-1}; MS (EI): *m/z* (%): 580 (3), 460 (9), 430 (4), 386 (3), 251 (4), 190 (4), 145 (6), 135 (11), 122 (24), 121 (100), 45 (6); HRMS (ESI): calcd for $C_{37}H_{55}NNaO_8Si$ $[M+Na]^+$: 692.35892; found: 692.35871.

(2*R*)-2-[(1*R*,3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-[(4-methoxybenzyl)oxy]-1-(methoxymethoxy)hexyl]-4-penten-1-ol (23): A solution of sodium borohydride (395 mg, 10.4 mmol) in water (10 mL) was added dropwise to a cooled (0 °C) solution of amide **22** (1.40 g, 2.09 mmol) in THF (20 mL). Stirring was continued for 12 h while the mixture was allowed to warm to room temperature. The solution was treated with saturated aqueous NH_4Cl solution (20 mL), stirred for 1 h, and transferred into a separation funnel. After extraction with ethyl acetate (3 × 20 mL), the combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue provided alcohol **23** (0.89 g, 86 %) as a colorless oil. $R_f = 0.49$ (petroleum ether/ethyl acetate, 2:1); $[\alpha]_D = +6.2$ ($c = 1.50$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta =$ 0.04, 0.05 (2 × s, 3H; Si(CH_3)$_2$), 0.87 (s, 9H; SiC(CH_3)$_3$), 1.39–1.49 (m, 1H; *H*-4′a), 1.53–1.69 (m, 4H; *H*-4′b, *H*-5′, *H*-2′a), 1.75 (ddd, *J* = 14.1, 8.1, 5.4 Hz, 1H; *H*-2′b), 1.89–2.07 (m, 3H; *H*-2, *H*-3), 2.69 (dd, *J* = 7.0, 4.7 Hz, 1H; O*H*), 3.37 (s, 3H; MOM C*H*$_3$), 3.42 (t, *J* = 6.4 Hz, 2H; *H*-6′), 3.60 (ddd, *J* = 11.2, 7.0, 4.3 Hz, 1H; *H*-1a), 3.67 (ddd, *J* = 11.2, 7.8, 4.7 Hz, 1H; *H*-1b), 3.75–3.84 (m, 2H; *H*-3′, *H*-1′), 3.79 (s, 3H; PMB C*H*$_3$), 4.41 (s, 2H; PMB C*H*$_2$), 4.60 (d, *J* = 6.7 Hz, 1H; MOM C*H*$_2$), 4.63 (d, *J* = 6.7 Hz, 1H; MOM C*H*$_2$), 5.00 (brd, *J* = 10.1 Hz, 1H; *H*-5a), 5.04 (brd, *J* = 17.1 Hz, 1H; *H*-5b), 5.76 (dddd, *J* = 17.1, 10.1, 6.8, 6.8 Hz, 1H; *H*-4), 6.86 (d, *J* = 8.6 Hz, 2H; PMB *H*-3,5), 7.24 ppm (d, *J* = 8.6 Hz, 2H; PMB *H*-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.4$ (Si(CH_3)$_2$), −4.4 (Si(CH_3)$_2$), 18.0 (Si*C*), 25.4 (*C*-5′), 25.9 (C(CH_3)$_3$), 31.5 (*C*-3), 33.3 (*C*-4′), 38.2 (*C*-2′), 42.6 (*C*-2), 55.3 (PMB CH$_3$), 56.0 (MOM CH$_3$), 63.5 (*C*-1), 69.2 (*C*-3′), 70.2 (*C*-6′), 72.5 (PMB CH$_2$), 76.9 (*C*-1′), 96.1 (MOM CH$_2$), 113.7 (PMB *C*-3,5), 116.4 (*C*-5), 129.2 (PMB *C*-2,6), 130.7 (PMB *C*-1), 136.8 (*C*-4), 159.1 ppm (PMB *C*-4); IR (film): $\tilde{\nu} = 1037$, 1096, 1249, 1361, 1464, 1513, 1613, 2856, 2887, 2929, 2952, 3074, 3470 cm^{-1}; MS (EI): *m/z* (%): 460 (2), 430 (3), 241 (5), 135 (11), 122 (10), 121 (100), 91 (3), 45 (3); HRMS (ESI): calcd for $C_{27}H_{48}NaO_6Si$ $[M+Na]^+$: 519.31124; found: 519.31153.

(2*R*)-2-[(1*R*,3*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-[(4-methoxybenzyl)oxy]-1-(methoxymethoxy)hexyl]-4-pentenyl 4-methylbenzenesulfonate (24): *p*-Toluenesulfonyl chloride (380 mg, 1.99 mmol) was added to a stirred solution of alcohol **23** (330 mg, 0.66 mmol) in pyridine (1.3 mL) at 0 °C. After being stirred for 12 h at room temperature, the reaction was quenched by addition of ice (0.2 g) and water (3 mL). The mixture was diluted with Et_2O (15 mL) and washed with saturated aqueous $NaHCO_3$ solution (3 mL), 1 N HCl (3 mL), and brine (3 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography gave the pure tosylate **24** (412 mg, 95 %) as a colorless oil. $R_f = 0.46$ (petroleum ether/ethyl acetate, 3:1); $[\alpha]_D = +8.6$ ($c = 1.50$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.02$ (s, 3H; Si(CH_3)$_2$a), 0.02 (s, 3H; Si(CH_3)$_2$b), 0.86 (s, 9H; SiC(CH_3)$_3$), 1.35–1.45 (m, 1H; *H*-4′a), 1.48–1.66 (m, 5H; *H*-4′b, *H*-2′, *H*-5′), 1.95–2.04 (m, 1H; *H*-2), 2.04–2.14 (m, 2H; *H*-3), 2.42 (s, 3H; Ts C*H*$_3$), 3.25 (s, 3H; MOM C*H*$_3$), 3.41 (t, *J* = 6.4 Hz, 2H; *H*-6′), 3.63–3.70 (m, 1H; *H*-1′), 3.70–3.80 (m, 1H; *H*-3′), 3.78 (s, 3H; PMB C*H*$_3$), 4.00 (dd, *J* = 9.4, 5.5 Hz, 1H; *H*-1a), 4.08 (dd, *J* = 9.4, 5.9 Hz, 1H; *H*-1b), 4.41 (s, 2H; PMB C*H*$_2$), 4.48 (d, *J* = 7.0 Hz, 1H; MOM C*H*$_2$a), 4.48 (d, *J* = 7.0 Hz, 1H; MOM C*H*$_2$b), 4.94–5.00 (m, 2H; *H*-5), 5.59–2.70 (m, 1H; *H*-4), 6.86 (d, *J* = 8.6 Hz, 2H; PMB *H*-3,5), 7.24 (d, *J* = 8.6 Hz, 2H; PMB *H*-2,6), 7.31 (d, *J* = 8.2 Hz, 2H; Ts *H*-3,5), 7.31 ppm (d, *J* = 8.2 Hz, 2H; Ts *H*-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.5$ (Si(CH_3)$_2$), 17.9 (Si*C*), 21.5 (Ts CH$_3$), 25.2 (*C*-5′), 25.8 (C(CH_3)$_3$), 30.8 (*C*-3), 33.1 (*C*-4′), 38.4 (*C*-2′), 41.0 (*C*-2), 55.1 (PMB CH$_3$), 55.7 (MOM CH$_3$), 69.0 (*C*-3′), 69.7 (*C*-1), 70.0 (*C*-6′), 72.4 (PMB CH$_2$), 74.7 (*C*-1′) 96.2 (MOM CH$_2$), 113.6 (PMB *C*-3,5), 117.0 (*C*-5), 127.8 (Ts *C*-2,6), 129.1 (PMB *C*-2,6), 129.7 (Ts *C*-3,5), 130.6 (PMB *C*-1), 132.9 (Ts *C*-1), 135.6 (*C*-4), 144.6 (Ts *C*-4), 159.0 ppm (PMB *C*-4); IR (film): $\tilde{\nu} = 1037$, 1097, 1178, 1249, 1364, 1513, 2855, 2929, 2952, 3070 cm^{-1}; MS (EI): *m/z* (%): 411 (2), 271 (3), 241 (10), 229 (46), 195 (5), 165 (8), 145 (14), 122 (14), 121 (100), 91 (13), 75 (12); HRMS (ESI): calcd for $C_{34}H_{54}NaO_8SSi$ $[M+Na]^+$: 673.32009; found: 673.32744.

(4*R*,6*R*,7*S*)-4-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-[(4-methoxybenzyl)oxy]-6-(methoxymethoxy)-7-methyl-9-decene (25): Lithium triethylborohydride (1 M solution in THF, 0.55 mL, 0.55 mmol) was added dropwise to a cooled (0 °C) solution of tosylate **24** (100 mg, 154 μmol) in THF (1.5 mL). Stirring was continued for 12 h while the mixture was allowed to warm to room temperature. After recooling to 0 °C, the reaction was quenched by careful addition of THF and water (1:1, 1 mL). The solution was treated with saturated aqueous NH_4Cl solution (2 mL) and allowed to warm to room temperature within 1 h while being stirring. The slurry was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography to yield methyl compound **25** (70 mg, 95 %) as a colorless oil. $R_f = 0.62$ (petroleum ether/ethyl acetate, 3:1); $[\alpha]_D = +17.4$ ($c = 1.29$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.04$, 0.05 (2 × s, 3 H each; $Si(CH_3)_2$), 0.86–0.89 (m, 3 H; CH_3), 0.88 (s, 9 H; $SiC(CH_3)_3$), 1.38–1.47 (m, 1 H; *H*-3a), 1.52 (ddd, $J = 14.1$, 8.2, 3.6 Hz, 1 H; *H*-5a), 1.57–1.75 (m, 4 H; *H*-3b, *H*-2, *H*-5b), 1.79–1.91 (m, 2 H; *H*-7, *H*-8a), 2.03–2.12 (m, 1 H; *H*-8b), 3.35 (s, 3 H; MOM CH_3), 3.42 (t, $J = 6.6$ Hz, 2 H; *H*-1), 3.48 (ddd, $J = 8.8$, 3.4, 3.4 Hz, 1 H; *H*-6), 3.79 (s, 3 H; PMB CH_3), 3.80–3.86 (m, 1 H; *H*-4), 4.42 (s, 2 H; PMB CH_2), 4.57 (d, $J = 6.9$ Hz, 1 H; MOM CH_2), 4.61 (d, $J = 6.9$ Hz, 1 H; MOM CH_2), 4.98 (br d, $J = 10.1$ Hz, 1 H; *H*-10a), 5.00 (br d, $J = 17.0$ Hz, 1 H; *H*-10b), 5.74 (dddd, $J = 17.0$, 10.1, 6.9, 6.9 Hz, 1 H; *H*-9), 6.86 (d, $J = 8.5$ Hz, 2 H; PMB *H*-3,5), 7.25 ppm (d, $J = 8.5$ Hz, 2 H; PMB *H*-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.5$ ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), 14.2 (CH_3), 18.0 (Si*C*), 25.4 (*C*-2), 25.9 ($C(CH_3)_3$), 32.9 (*C*-3), 35.9 (*C*-7), 37.1 (*C*-8), 37.7 (*C*-5), 55.2 (PMB CH_3), 55.7 (MOM CH_3), 69.5 (*C*-4), 70.3 (*C*-1), 72.4 (PMB CH_2), 78.2 (*C*-6), 95.7 (MOM CH_2), 113.7 (PMB *C*-3,5), 115.8 (*C*-10), 129.1 (PMB *C*-2,6), 130.7 (PMB *C*-1), 137.4 (*C*-9), 159.0 ppm (PMB *C*-4); IR (film): $\tilde{\nu} = 1039$, 1097, 1249, 1512, 2856, 2889, 2930, 2953 cm^{-1}; MS (EI): *m*/*z* (%): 271 (4), 241 (3), 203 (3), 122 (13), 121 (100); HRMS (ESI): calcd for $C_{27}H_{48}NaO_5Si$ $[M+Na]^+$: 503.31632; found: 503.31641.

(4*R*,6*R*,7*S*)-1-[(4-Methoxybenzyl)oxy]-6-(methoxymethoxy)-7-methyl-9-decen-4-ol (26): TBAF (1 M in THF, 0.89 mL, 0.89 mmol) was added to a solution of TBDMS ether **25** (142 mg, 295 μmol) in THF (3 mL) at 0 °C. After being stirred for 15 h, the solution was treated with saturated aqueous $NaHCO_3$ solution (2 mL) and the mixture was extracted with Et_2O (3 × 5 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography of the residue gave the desired alcohol **26** (107 mg, 99 %) as a colorless oil. $R_f = 0.36$ (petroleum ether/ethyl acetate, 2:1); $[\alpha]_D = +29.1$ ($c = 1.16$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.89$ (d, $J = 6.5$ Hz, 3 H; CH_3), 1.47–1.64 (m, 4 H; *H*-3, *H*-5), 1.67–1.78 (m, 2 H; *H*-2), 1.83–1.97 (m, 2 H; *H*-8a, *H*-7), 1.99–2.06 (m, 1 H; *H*-8b), 3.40 (s, 3 H; MOM CH_3), 3.48 (td, $J = 6.2$, 2.3 Hz, 2 H; *H*-1), 3.53 (br s, 1 H; O*H*), 3.72 (ddd, $J = 9.6$, 3.6, 3.6 Hz, 1 H; *H*-6), 3.74–3.79 (m, 1 H; *H*-4), 3.80 (s, 3 H; PMB CH_3), 4.44 (s, 2 H; PMB CH_2), 4.63 (d, $J = 6.8$ Hz, 1 H; MOM CH_2), 4.72 (d, $J = 6.8$ Hz, 1 H; MOM CH_2), 5.00 (br d, $J = 10.4$ Hz, 1 H; *H*-10a), 5.01 (br d, $J = 17.0$ Hz, 1 H; *H*-10b), 5.75 (dddd, $J = 17.0$, 10.4, 6.8, 6.8 Hz, 1 H; *H*-9), 6.87 (d, $J = 8.6$ Hz, 2 H; PMB *H*-3,5), 7.26 ppm (d, $J = 8.6$ Hz, 2 H; PMB *H*-2,6); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.5$ (CH_3), 25.8 (*C*-2), 34.4 (*C*-3), 35.2 (*C*-7), 36.0 (*C*-5), 37.5 (*C*-8), 55.1 (PMB CH_3), 55.9 (MOM CH_3), 70.1 (*C*-1), 70.8 (*C*-4), 72.5 (PMB CH_2), 81.0 (*C*-6), 95.3 (MOM CH_2), 113.6 (PMB *C*-3,5), 116.0 (*C*-10), 129.2 (PMB *C*-2,6), 130.4 (PMB *C*-1), 136.9 (*C*-9), 159.0 ppm (PMB *C*-4); IR (film): $\tilde{\nu} = 1037$, 1096, 1248, 1513, 1613, 2860, 2934, 3075, 3463 cm^{-1}; MS (EI): *m*/*z* (%): 203 (3), 185 (4), 137 (44), 122 (12), 121 (100), 84 (21), 49 (15); HRMS (ESI): calcd for $C_{21}H_{34}NaO_5$ $[M+Na]^+$: 389.22985; found: 389.22996.

(1*S*,3*R*,4*S*)-1-{3-[(4-Methoxybenzyl)oxy]propyl}-3-(methoxymethoxy)-4-methyl-6-heptenyl 2-allyl-6-methoxybenzoate (28): A solution of acid[11g] **27** (246 mg, 1.28 mmol) and DIAD (129 μL, 132 mg, 654 μmol) in toluene (3 mL) was added dropwise to a solution of alcohol **26** (94 mg, 256 μmol) and triphenylphosphine (168 mg, 641 μmol) in toluene (3 mL). After the mixture was stirred for 3 h at room temperature, the solvent was removed and the residue was purified by flash chromatography. Ester **28** (98 mg, 71 %) was isolated as a pale-yellow oil. $R_f = 0.62$ (petroleum ether/ethyl acetate, 2:1); $[\alpha]_D = +2.3$ ($c = 1.03$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.90$ (d, $J = 6.7$ Hz, 3 H; CH_3), 1.63–1.70 (m, 2 H; *H*-2′), 1.71–1.86 (m, 5 H; *H*-2″, *H*-1″, *H*-5′a), 1.88–1.98 (m, 1 H; *H*-4′), 2.06 (br dd, $J = 13.4$, 6.1 Hz, 1 H; *H*-5′b), 3.37 (br d, $J = 6.5$ Hz, 2 H; *H*-7), 3.40 (s, 3 H; MOM CH_3), 3.48 (br t, $J = 6.2$ Hz, 2 H; *H*-3″), 3.70 (ddd, $J = 9.0$, 3.3, 3.3 Hz, 1 H; *H*-3″), 3.80 (s, 3 H; PMB CH_3), 3.80 (s, 3 H; Ph−OCH_3), 4.44 (s, 2 H; PMB CH_2), 4.70 (d, $J = 6.8$ Hz, 1 H; MOM CH_2), 4.73 (d, $J = 6.8$ Hz, 1 H; MOM CH_2), 4.91 (br d, $J = 10.1$ Hz, 1 H; *H*-7′a), 4.96 (br d, $J = 17.1$ Hz, 1 H; *H*-7′b), 5.05 (br d, $J = 17.7$ Hz, 1 H; *H*-9a), 5.05 (br d, $J = 11.2$ Hz, 1 H; *H*-9b), 5.31–5.38 (m, 1 H; *H*-1′), 5.74 (dddd, $J = 17.1$, 10.1, 7.3 Hz, 1 H; *H*-6′), 5.94 (dddd, $J = 17.7$, 11.2, 6.5 Hz, 1 H; *H*-8), 6.77 (br d, $J = 8.4$ Hz, 1 H; *H*-5), 6.82 (br d, $J = 7.7$ Hz, 1 H; *H*-3), 6.87 (d, $J = 8.6$ Hz, 2 H; PMB *H*-3,5), 7.26 (d, $J = 8.6$ Hz, 2 H; PMB *H*-2,6), 7.27 ppm (dd, $J = 8.4$, 7.7 Hz, 1 H; *H*-4); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 13.6 (CH_3), 25.3 (*C*-2″), 31.8 (*C*-1″), 34.7 (*C*-2′), 36.5 (*C*-4′), 37.2 (*C*-7), 37.6 (*C*-5′), 55.2 (PMB CH_3), 55.5 (Ph−OCH_3), 55.7 (MOM CH_3), 69.8 (*C*-3″), 72.4 (*C*-1′), 72.5 (PMB CH_2), 78.3 (*C*-3′), 97.0 (MOM CH_2), 108.7 (*C*-5), 113.7 (PMB *C*-3,5), 115.8 (*C*-7′), 116.3 (*C*-9), 121.5 (*C*-3), 124.2 (*C*-1), 129.2 (PMB *C*-2,6), 130.1 (*C*-4), 130.7 (PMB *C*-1), 136.4 (*C*-8), 137.1 (*C*-6′), 138.1 (*C*-2), 156.2 (*C*-6), 159.1 (PMB *C*-4), 168.0 ppm (Ph−CO_2); IR (film): $\tilde{\nu} = 1038$, 1100, 1247, 1266, 1469, 1513, 1585, 1724, 2843, 2932, 3075 cm^{-1}; MS (EI): *m*/*z* (%): 495 (4), 303 (3), 203 (11), 175 (45), 121 (100); HRMS (ESI): calcd for $C_{32}H_{44}NaO_7$ $[M+Na]^+$: 563.29792; found: 563.29916.

(3*S*,5*R*,6*S*)-5,14-Dihydroxy-3-(3-hydroxypropyl)-6-methyl-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (30): 9-I-9-BBN (1 M solution in *n*-hexane, 206 μL, 206 μmol) was added to a solution of macrolactone **19** (55.0 mg, 107 μmol) in CH_2Cl_2 (2.1 mL) quickly through a syringe. After 90 s, methanol (3 mL) was added and stirring was then continued for 1 h. The solvent was removed under reduced pressure and the residue was treated again with methanol (3 mL). This process was repeated twice whereafter the crude product could be used in the next step without further purification. For analytical purposes, purification was performed by flash chromatography to yield triol **30** (18.7 mg, 52 %) as a colorless viscous oil. $R_f = 0.40$ (petroleum ether/ethyl acetate, 1:5); $[\alpha]_D = +13.8$ ($c = 0.70$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.91$ (d, $J = 6.8$ Hz, 3 H; CH_3), 1.37 (dd, $J = 15.0$, 8.7 Hz, 1 H; *H*-14a), 1.63–1.87 (m, 7 H; *H*-17, C-13-O*H*, C-18-O*H*, *H*-16, *H*-11a), 1.87–1.94 (m, 1 H; *H*-12), 1.99 (dd, $J = 15.0$, 10.8 Hz, 1 H; *H*-14b), 2.29–2.38 (m, 1 H; *H*-11b), 3.38 (br d, $J = 16.6$ Hz, 1 H; *H*-8a), 3.64 (dd, $J = 8.7$, 3.1 Hz, 1 H; *H*-13), 3.70 (td, $J = 6.1$, 1.7 Hz, 2 H; *H*-18), 3.75 (dd, $J = 16.6$, 5.6 Hz, 1 H; *H*-8b), 5.04–5.15 (m, 1 H; *H*-10), 5.47 (br d, $J = 15.3$ Hz, 1 H; *H*-9), 5.55 (br dt, $J = 10.8$, 5.3 Hz, 1 H; *H*-15), 6.69 (dd, $J = 7.4$, 0.9 Hz, 1 H; *H*-6), 6.88 (dd, $J = 8.3$, 0.9 Hz, 1 H; *H*-4), 7.29 ppm (dd, $J = 8.3$, 7.4 Hz, 1 H; *H*-5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 13.7$ (CH_3), 28.0 (*C*-17), 32.0 (*C*-16), 35.8 (*C*-14), 37.2 (*C*-12), 38.4 (*C*-11), 39.1 (*C*-8), 62.4 (*C*-18), 70.6 (*C*-13), 74.8 (*C*-15), 116.7 (*C*-4), 123.3 (*C*-2), 123.5 (*C*-6), 126.6 (*C*-10), 132.8 (*C*-9), 133.9 (*C*-5), 142.2 (*C*-7), 162.4 (*C*-3), 171.3 ppm (*C*-1); IR (film): $\tilde{\nu} = 1019$, 1065, 1120, 1294, 1345, 1465, 1588, 1695, 2874, 2926, 2955, 3320 cm^{-1}; MS (EI): *m*/*z* (%): 334 (6), 317 (7), 316 (11), 298 (15), 246 (6), 239 (6), 231 (16), 213 (18), 196 (30), 181 (37), 173 (43), 172 (100), 147 (32), 115 (28), 97 (27), 71 (42), 43 (74); HRMS (EI): calcd for $C_{19}H_{26}O_5$ $[M]^+$: 334.1780; found: 334.1811.

(3*S*,5*R*,6*S*)-5,14-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-(3-{[*tert*-butyl(dimethyl)silyl]oxy}propyl)-6-methyl-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (31): TBDMSCl (298 mg, 1.97 mmol) was added to a stirred solution of crude triol **30**, imidazole (168 mg, 2.47 mmol), and DMAP (12.1 mg, 98.7 μmol) in dry DMF (2.2 mL). The resulting solution was stirred at ambient temperature for 4 d, then diluted with H_2O (5 mL) and extracted with Et_2O (3 × 10 mL). The combined extracts were washed with 0.1 N HCl (10 mL) and brine (10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography to give the desired ether **31** (40.1 mg, 60 % from macrolactone **19**) as a colorless viscous oil. $R_f = 0.45$ (petroleum ether/diethyl ether, 20:1); $[\alpha]_D = +8.7$ ($c = 0.53$, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 0.03$ (s, 6 H; $Si(CH_3)_2$), 0.11 (s, 3 H; $Si(CH_3)_2$), 0.15 (s, 3 H; $Si(CH_3)_2$), 0.16 (s, 3 H; $Si(CH_3)_2$), 0.22 (s, 3 H; $Si(CH_3)_2$), 0.83 (d, $J = 6.6$ Hz, 3 H; CH_3), 0.88 (s, 9 H; $SiC(CH_3)_3$), 0.91 (s, 9 H; $SiC(CH_3)_3$), 0.96 (s, 9 H; $SiC(CH_3)_3$), 1.40 (dd, $J = 15.1$, 8.9 Hz, 1 H; *H*-14a), 1.56–1.62 (m, 2 H; *H*-17), 1.62–1.74 (m, 4 H; *H*-14b, *H*-16, *H*-11a), 1.76–1.84 (m, 1 H; *H*-12), 2.25 (br d, $J = 12.3$ Hz, 1 H; *H*-11b), 3.31 (br d, $J = 16.3$ Hz, 1 H; *H*-8a), 3.55–3.69 (m, 2 H; *H*-18), 3.66 (dd, $J = 16.3$, 9.1 Hz, 1 H; *H*-8b), 4.27 (dd, $J = 8.9$, 3.0 Hz, 1 H; *H*-13), 5.12–5.19 (m, 1 H; *H*-15), 5.30–5.46 (m, 2 H; *H*-9, *H*-10), 6.70 (d, $J = 8.3$ Hz, 1 H; *H*-4), 6.72 (d, $J = 7.7$ Hz, 1 H; *H*-6), 7.09 ppm (dd, $J = 8.3$, 7.7 Hz, 1 H; *H*-5); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ −5.3 ($Si(CH_3)_2$), −4.5 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), −4.2 ($Si(CH_3)_2$), 13.1 (CH_3), 18.0 (Si*C*), 18.3 (Si*C*), 18.4 (Si*C*), 25.7 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 26.0 ($SiC(CH_3)_3$), 28.9 (*C*-17), 32.3 (*C*-16), 36.5 (*C*-14), 37.1 (*C*-12), 38.0 (*C*-11), 38.2 (*C*-8), 63.1 (*C*-18), 72.0 (*C*-13), 74.9 (*C*-15), 118.0 (*C*-4), 123.2 (*C*-6), 127.8 (*C*-2), 128.2 (*C*-9), 129.3 (*C*-5), 131.3 (*C*-10), 138.6 (*C*-7), 152.7 (*C*-3), 168.4 ppm (*C*-1); IR (film): $\tilde{\nu}$ = 1067, 1098, 1254, 1278, 1456, 1585, 1723, 2857, 2898, 2929, 2955 cm^{-1}; MS (EI): *m/z* (%): 619 (22), 602 (7), 527 (6), 487 (24), 419 (42), 395 (11), 355 (18), 337 (20), 299 (23), 247 (22), 203 (25), 149 (59), 147 (100), 133 (74), 109 (67), 75 (80), 73 (97); HRMS (EI): calcd for $C_{33}H_{59}O_5Si_3$ $[M-t\mathrm{Bu}]^+$: 619.36701; found: 619.36946; HRMS (FAB): calcd for $C_{37}H_{68}O_5NaSi_3$ $[M+\mathrm{Na}]^+$: 699.42723; found: 699.42184.

(3*S*,5*R*,6*S*)-5,14-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-3-(3-hydroxypropyl)-6-methyl-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-1-one (32): A cooled (0 °C) solution of silyl ether **31** (50.0 mg, 73.8 μmol) in CH_2Cl_2 (3.0 mL) and methanol (1.0 mL) was treated with CSA (0.03 M solution in methanol, 492 μL, 14.8 μmol) with stirring. The resulting mixture was stirred for 1.5 h before the reaction was quenched by addition of saturated aqueous $NaHCO_3$ solution (5.0 mL). The slurry was extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography of the residue provided recovered starting material **31** (4.9 mg, 10%) and primary alcohol **32** (35.2 mg, 85%) as a colorless viscous oil. R_f = 0.57 (petroleum ether/ethyl acetate, 4:1); $[\alpha]_D$ = +13.5 (*c* = 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.11 (s, 3H; $Si(CH_3)_2$), 0.15 (s, 3H; $Si(CH_3)_2$), 0.16 (s, 3H; $Si(CH_3)_2$), 0.21 (s, 3H; $Si(CH_3)_2$), 0.83 (d, *J* = 6.7 Hz, 3H; CH_3), 0.91 (s, 9H; $SiC(CH_3)_3$), 0.95 (s, 9H; $SiC(CH_3)_3$), 1.39 (dd, *J* = 15.2, 9.0 Hz, 1H; *H*-14a), 1.46 (brs, 1H; O*H*), 1.62–1.75 (m, 6H; *H*-17 *H*-14b, *H*-11a, *H*-16), 1.75–1.85 (m, 1H; *H*-12), 2.25 (brd, *J* = 12.9 Hz, 1H; *H*-11b), 3.31 (brd, *J* = 16.5 Hz, 1H; *H*-8a), 3.60–3.69 (m, 2H; *H*-18), 3.65 (dd, *J* = 16.5, 9.2 Hz, 1H; *H*-8b), 4.27 (dd, *J* = 9.0, 3.4 Hz, 1H; *H*-13), 5.17–5.23 (m, 1H; *H*-15), 5.32 (brdd, *J* = 15.2, 9.2 Hz, 1H; *H*-9), 5.41 (brdd, *J* = 15.2, 10.2 Hz, 1H; *H*-10), 6.71 (d, *J* = 8.4 Hz, 1H; *H*-4), 6.73 (d, *J* = 7.9, 1H; *H*-6), 7.10 ppm (dd, *J* = 8.4, 7.9 Hz, 1H; *H*-5); ^{13}C NMR (100 MHz, $CDCl_3$): δ = −4.6 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), −4.4 ($Si(CH_3)_2$), −4.3 ($Si(CH_3)_2$), 13.0 (CH_3), 18.0 (Si*C*), 18.3 (Si*C*), 25.7 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 28.4 (*C*-17), 32.0 (*C*-16), 36.3 (*C*-14), 37.0 (*C*-12), 38.0 (*C*-11), 38.2 (*C*-8), 62.7 (*C*-18), 72.0 (*C*-13), 74.6 (*C*-15), 118.1 (*C*-4), 123.3 (*C*-6), 127.8 (*C*-2), 128.3 (*C*-9), 129.4 (*C*-5), 131.3 (*C*-10), 138.6 (*C*-7), 152.6 (*C*-3), 168.3 ppm (*C*-1); MS (EI): *m/z* (%): 505 (38), 487 (60), 419 (19), 373 (53), 355 (98), 299 (37), 247 (58), 203 (56), 151 (54), 133 (73), 85 (38), 75 (81), 73 (100); IR (film): $\tilde{\nu}$ = 1026, 1066, 1116, 1254, 1281, 1457, 1581, 1724, 2857, 2894, 2929, 2954, 3430 cm^{-1}; HRMS (EI): calcd for $C_{27}H_{45}O_5Si_2$ $[M-t\mathrm{Bu}]^+$: 505.28054; found: 505.28262; HRMS (FAB): calcd for $C_{31}H_{54}O_5NaSi_2$ $[M+\mathrm{Na}]^+$: 585.354075; found: 585.34224.

3-((3*S*,5*R*,6*S*)-5,14-Bis{[*tert*-butyl(dimethyl)silyl]oxy}-6-methyl-1-oxo-3,4,5,6,7,10-hexahydro-1*H*-2-benzoxacyclododecin-3-yl)propanal (33): A cooled (0 °C) solution of primary alcohol **32** (26.5 mg, 47.0 mmol) in CH_2Cl_2 (4.0 mL) was treated with NMO (8.0 mg, 68.3 mmol), molecular sieves (4) Å, 20 mg), and TPAP (2.1 mg, 5.9 mmol) in turn. The resulting slurry was stirred 1 h at 0 °C and filtered over a short pad of silica gel (petroleum ether/ethyl acetate, 2:1) to yield aldehyde **33** (24.0 mg, 91%) as a pale-yellow oil. R_f = 0.75 (petroleum ether/ethyl acetate, 5:1); $[\alpha]_D$ = +12.0 (*c* = 1.00, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.06, 0.16, 0.28, 0.46 (4 × s, 3H each; $Si(CH_3)_2$), 0.87 (d, *J* = 6.8 Hz, 3H; CH_3), 0.98 (s, 9H; $SiC(CH_3)_3$), 1.10 (s, 9H; $SiC(CH_3)_3$), 1.27 (dd, *J* = 15.0, 9.0 Hz, 1H; *H*-14a), 1.57–1.65 (m, 1H; *H*-11a), 1.60 (dd, *J* = 15.0, 8.6 Hz, 1H; *H*-14b), 1.72–1.81 (m, 1H; *H*-12), 1.82–1.99 (m, 2H; *H*-16), 2.11 (brdt, *J* = 14.3, 4.6 Hz, 1H; *H*-11b), 2.14–2.24 (m, 2H; *H*-17), 3.20 (dd, *J* = 16.2, 4.0 Hz, 1H; *H*-8a), 3.68 (brdd, *J* = 16.2, 8.3 Hz, 1H; *H*-8b), 4.45 (dd, *J* = 8.8, 3.5 Hz, 1H; *H*-13), 5.32–5.42 (m, 3H; *H*-10, *H*-9, *H*-15), 6.56 (d, *J* = 7.6 Hz, 1H; *H*-6), 6.68 (brd, *J* = 8.2, 1H; *H*-4), 6.90 (dd, *J* = 8.2, 7.6 Hz, 1H; *H*-5), 9.39 ppm (brs, 1H; *H*-18); ^{13}C NMR (100 MHz, C_6D_6): δ = −4.4 ($Si(CH_3)_2$), −4.3 ($Si(CH_3)_2$), −4.1 ($Si(CH_3)_2$), −4.0 ($Si(CH_3)_2$), 13.2 (CH_3), 18.3 (Si*C*), 18.6 (Si*C*), 25.9 ($C(CH_3)_3$), 26.2 ($C(CH_3)_3$), 28.5 (*C*-16), 36.8 (*C*-14), 37.4 (*C*-12), 38.2 (*C*-11), 38.6 (*C*-18), 39.8 (*C*-17), 72.3 (*C*-13), 73.4 (*C*-15), 118.6 (*C*-4), 123.7 (*C*-6), 128.8 (*C*-2), 128.8 (*C*-9), 129.5 (*C*-5), 131.4 (*C*-10), 138.9 (*C*-7), 153.3 (*C*-3), 168.3 (*C*-1), 199.4 ppm (*C*-18); IR (film): $\tilde{\nu}$ = 1022, 1066, 1115, 1254, 1457, 1581, 1726, 2713, 2857, 2892, 2929 cm^{-1}; MS (FAB): *m/z* (%): 737 (8), 683 (22), 624 (5), 584 (8), 561 (9), 543 (17), 504 (24), 411 (30), 353 (21), 287 (35), 203 (49), 136 (100); HRMS (EI): calcd for $C_{27}H_{43}O_5Si_2$ $[M-t\mathrm{Bu}]^+$: 503.26489; found: 503.26671.

Bis[*tert*-butyl(dimethyl)silyl]-salicylihalamide-hemiaminal (35): DIBAL (1.0 M in hexane, 0.149 mL) was added dropwise to a well-stirred solution of (2*Z*,4*Z*)-hepta-2,4-dienamide (**34**) (15.1 mg, 0.121 mmol) in dry THF (1.0 mL) at 0 °C. After the mixture had been stirred for 30 min at 0 °C, a solution of aldehyde **33** (32.9 mg, 0.0587 mmol) in dry THF (0.25 mL) was added. The resulting solution was stirred overnight at 0 °C, before it was diluted with ethyl acetate (5 mL) and quenched with buffer (pH 7, 5 mL) at 0 °C. After separation of the layers, the aqueous layer was extracted with ethyl acetate (4 × 3 mL). The combined organic layers were washed with brine (1 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 4:1) gave unreacted aldehyde **33** (10.5 mg, 32%) and **35** (24.5 mg, 61%) as a mixture of diastereomers (approximately 1:1) as a colorless oil. R_f = 0.41 (petroleum ether/ethyl acetate, 4:1); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.11, 0.12 (2 × s, 3H; $SiCH_3$), 0.19 (2 peaks, s, 2 × 1.5H; $SiCH_3$), 0.30 (s, 1.5H; $SiCH_3$), 0.31 (s, 1.5H; $SiCH_3$), 0.50 (s, 3H; $SiCH_3$), 0.79 (2 peaks, t, *J* = 7.6 Hz, 3H; *H*-25), 0.90 (d, *J* = 6.3 Hz, 1.5H; CH_3), 0.91 (d, *J* = 6.3 Hz, 1.5H; CH_3), 1.02 (2 peaks, s, 2 × 4.5H; $C(CH_3)_3$), 1.11 (s, 9H; $C(CH_3)_3$), 1.41–1.50 (m, 1H; *H*-14a), 1.58–1.85 (m, 7H; *H*-11a, *H*-16, *H*-17, *H*-14b, *H*-12), 1.99 (dq, *J* = 8.6, 7.6 Hz, 2H; *H*-24), 2.09–2.16 (m, 1H; *H*-11b), 3.22 (dd, *J* = 16.3, 3.8 Hz, 1H; *H*-8a), 3.22 (dd, *J* = 16.3, 8.1 Hz, 1H; *H*-8b), 3.85 (brs, 0.5H; O*H*), 3.97 (brs, 0.5H; O*H*), 4.49–4.53 (m, 1H; *H*-15), 5.12 (d, *J* = 11.5 Hz, 1H; *H*-20), 5.36–5.41 (m, 2H; *H*-10, *H*-9), 5.43–5.51 (m, 2H; *H*-18, *H*-13), 5.51–5.59 (brm, 1H; N*H*), 5.61–5.67 (m, 1H; *H*-23), 6.57 (d, *J* = 7.6 Hz, 1H; *H*-6), 6.62 (dd, *J* = 11.9, 11.5 Hz, 1H; *H*-21), 6.71 (d, *J* = 7.9 Hz, 0.5H; *H*-4), 6.72 (d, *J* = 7.9 Hz, 0.5H; *H*-4), 6.95 (dd, *J* = 7.9, 7.6 Hz, 1H; *H*-5), 7.85–7.93 ppm (m, 1H; H-22); ^{13}C NMR (100 MHz, C_6D_6): δ = −4.4 (2 peaks, $SiCH_3$), −4.2 (3 peaks, $SiCH_3$), −4.1 ($SiCH_3$), −3.9 ($SiCH_3$), −3.8 ($SiCH_3$), 13.3 (CH_3), 14.0 (*C*-25), 18.4 (2 peaks, Si*C*), 18.6 (2 peaks, Si*C*), 20.8 (*C*-24), 26.0 (2 peaks, $C(CH_3)_3$), 26.3 (2 peaks, $C(CH_3)_3$), 31.1 (*C*-17), 31.5 (*C*-16), 31.7 (*C*-16), 36.9 (*C*-14), 37.5 (*C*-12), 37.6 (*C*-12), 38.2 (*C*-11), 38.6 (2 peaks, *C*-8), 72.4 (*C*-15), 74.2 (2 peaks, *C*-13), 74.6 (*C*-18), 74.9 (*C*-18), 118.5 (*C*-4), 118.6 (*C*-4), 120.1 (*C*-20), 123.6 (*C*-6), 124.8 (*C*-22), 128.7 (*C*-9), 128.8 (*C*-9), 128.9 (*C*-2), 129.5 (*C*-5), 131.5 (*C*-10), 136.3 (*C*-21), 136.4 (*C*-21), 138.9 (*C*-7), 141.4 (*C*-23), 153.3 (2 peaks, *C*-3), 166.9 (*C*-19), 168.4 ppm (*C*-1); IR (film): $\tilde{\nu}$ = 1006, 1029, 1067, 1117, 1225, 1265, 1361, 1381, 1457, 1501, 1581, 1593, 1628, 1663, 1724, 2857, 2897, 2930, 2956, 3317, 3421 cm^{-1}; HRMS (ESI): calcd for $C_{38}H_{63}NNaO_6Si_2$ $[M+\mathrm{Na}]^+$: 708.40861; found: 708.40864.

Bis[*tert*-butyl(dimethyl)silyl]-salicylihalamide (36): Dry pyridine (0.085 mL, 1.05 mmol) and dry acetic anhydride (0.050 mL, 0.525 mmol) were added to a stirred solution of hemiaminal **35** (24 mg, 0.035 mmol) in dry THF (1.0 mL). The resulting mixture was stirred for 24 h at room temperature and was then heated to reflux for 48 h. After the solution had cooled to room temperature, it was treated with buffer (pH 7, 2.5 mL), the phases were separated, and the aqueous layer was extracted with diethyl ether (4 × 1.5 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (1.5 mL) and buffer (pH 7, 1.5 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by rapid flash chromatography (petroleum ether/ethyl acetate, 30:1, containing 0.2% of NEt_3) gave *cis*-di-TBDMS-salicylihalamide (*Z*)-**36** (3.3 mg, 14%) and *trans*-di-TBDMS-salicylihalamide (*E*)-**36** (10.5 mg, 45%), both as colorless oils.

*Compound (Z)-**36** (minor product)*: R_f = 0.28 (petroleum ether/ethyl acetate, 20:1, with 0.2% NEt_3); $[\alpha]_D$ = −64.9 (*c* = 0.37, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6): δ = 0.10, 0.15, 0.28, 0.44 (4 × s, 3H each; $SiCH_3$), 0.79 (t, *J* = 7.6 Hz, 3H; *H*-25), 0.88 (d, *J* = 6.8 Hz, 3H; CH_3), 0.97 (s, 9H; $C(CH_3)_3$), 1.11 (s, 9H; $C(CH_3)_3$), 1.38–1.47 (m, 1H; *H*-14a), 1.53–1.63 (m, 1H; *H*-11a), 1.71–1.77 (m, 1H; *H*-12), 1.75–1.82 (m, 1H; *H*-14b), 2.02 (dq, *J* = 8.6, 7.6 Hz, 2H; *H*-24), 2.03–2.07 (m, 1H; *H*-11b), 2.11–2.20 (m, 1H; *H*-16a), 2.50–2.57 (m, 1H; *H*-16b), 3.14 (d, *J* = 16.4 Hz, 1H; *H*-8a), 3.62 (dd, *J* = 16.4, 7.1 Hz, 1H; *H*-8b), 4.44–4.47 (m, 1H; *H*-15), 4.65 (ddd, *J* = 8.6, 8.3, 8.3 Hz, 1H; *H*-17), 5.19–5.26 (m, 1H; *H*-9), 5.27–5.36 (m, 1H; *H*-10), 5.47 (d, *J* = 11.4 Hz, 1H; *H*-20), 5.56–5.63 (m, 1H; *H*-15), 5.57–5.64 (m, 1H; *H*-23), 6.53 (d, *J* = 7.6 Hz, 1H; *H*-6), 6.75 (d, *J* = 7.9 Hz, 1H; *H*-4), 6.76 (dd, *J* = 11.9, 11.4 Hz, 1H; *H*-21), 6.91 (dd, *J* = 7.9, 7.8 Hz, 1H; *H*-5), 7.32–7.37 (m, 1H; *H*-18), 7.81–7.88 (brm, 1H; N*H*), 8.03 ppm (dd, *J* = 11.6, 11.4 Hz, 1H; *H*-22); ^{13}C NMR (100 MHz, C_6D_6): δ = −4.4 (2 peaks, $SiCH_3$), −4.1 ($SiCH_3$), −4.0 ($SiCH_3$), 13.2 (CH_3), 14.0 (*C*-25), 18.4 (Si*C*), 18.5 (Si*C*), 20.8 (*C*-24), 25.8 ($C(CH_3)_3$), 26.2 ($C(CH_3)_3$), 32.7

(*C*-16), 37.6 (*C*-14), 38.0 (*C*-12), 38.5 (*C*-11), 38.7 (*C*-8), 72.4 (*C*-13), 75.0 (*C*-15), 103.6 (*C*-17), 118.7 (*C*-4), 120.0 (*C*-20), 124.3 (*C*-6), 125.2 (*C*-22), 125.8 (*C*-18), 127.9 (*C*-9), 128.8 (*C*-2), 129.7 (*C*-5), 131.9 (*C*-10), 136.8 (*C*-21), 139.5 (*C*-7), 141.3 (*C*-23), 152.7 (*C*-3), 163.0 (*C*-19), 168.1 ppm (*C*-1); IR (film): $\tilde{\nu}$ = 1022, 1066, 1113, 1199, 1260, 1381, 1456, 1485, 1593, 1657, 1727, 2856, 2928, 2958, 3394 cm^{-1}; HRMS (ESI): calcd for $C_{38}H_{61}NNaO_5Si_2$ [*M*+Na]$^+$: 690.39805; found: 690.39870.

*Compound (*E*)-**36** (main product)*: R_f = 0.19 (petroleum ether/ethyl acetate, 20:1, with 0.2% NEt$_3$); $[\alpha]_D$ = −11.0 (*c* = 1.23, CH$_2$Cl$_2$); ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 0.12, 0.17, 0.31, 0.51 (4×s, 3H each; SiC*H*$_3$), 0.77 (t, *J* = 7.6 Hz, 3H; *H*-25), 0.88 (d, *J* = 6.8 Hz, 3H; C*H*$_3$), 1.04 (s, 9H; C(C*H*$_3$)$_3$), 1.11 (s, 9H; C(C*H*$_3$)$_3$), 1.56 (ddd, *J* = 15.1, 8.9, 8.8 Hz, 1H; *H*-14a), 1.63–1.68 (m, 1H; *H*-11a), 1.70 (ddd, *J* = 15.1, 8.9, 8.8 Hz, 1H; *H*-14a), 1.75–1.83 (m, 1H; *H*-12), 1.97 (dq, *J* = 8.8, 7.6 Hz, 2H; *H*-24), 2.08–2.15 (m, 1H; *H*-11b), 2.41–2.53 (m, 2H; *H*-16), 3.22 (dd, *J* = 16.4, 4.0 Hz, 1H; *H*-8a), 3.72 (dd, *J* = 16.4, 8.6 Hz, 1H; *H*-8b), 4.50–4.53 (m, 1H; *H*-13), 4.94 (ddd, *J* = 14.2, 7.6, 7.1 Hz, 1H; *H*-17), 5.00 (d, *J* = 11.4 Hz, 1H; *H*-20), 5.34–5.39 (m, 1H; *H*-10), 5.38–5.43 (m, 1H; *H*-9), 5.48–5.55 (m, 1H; *H*-15), 5.57–5.64 (m, 1H; *H*-23), 6.16 (brd, *J* = 10.8 Hz, 1H; N*H*), 6.58 (d, *J* = 7.9 Hz, 1H; *H*-6), 6.59 (dd, *J* = 11.9, 11.4 Hz, 1H; *H*-21), 6.72 (d, *J* = 8.1 Hz, 1H; *H*-4), 6.91 (dd, *J* = 8.1, 7.9 Hz, 1H; *H*-5), 7.21 (dd, *J* = 14.2, 10.8 Hz, 1H; *H*-18), 7.94 ppm (dd, *J* = 11.6, 11.4 Hz, 1H; *H*-22); ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = −4.4 (Si*C*H$_3$), −4.3 (Si*C*H$_3$), −4.1 (Si*C*H$_3$), −3.9 (Si*C*H$_3$), 13.2 (*C*H$_3$), 14.0 (*C*-25), 18.4 (Si*C*), 18.5 (Si*C*), 20.8 (*C*-24), 25.9 (C(*C*H$_3$)$_3$), 26.3 (C(*C*H$_3$)$_3$), 36.2 (*C*-14), 36.6 (*C*-16), 37.7 (*C*-12), 38.2 (*C*-11), 38.5 (*C*-8), 67.8 (*C*-13), 72.4 (*C*-15), 106.4 (*C*-17), 118.3 (*C*-4), 119.7 (*C*-20), 123.6 (*C*-6), 125.0 (*C*-22), 125.9 (*C*-18), 128.8 (*C*-9), 129.0 (*C*-2), 129.5 (*C*-5), 131.5 (*C*-10), 136.7 (*C*-21), 139.0 (*C*-7), 141.4 (*C*-23), 153.3 (*C*-3), 162.3 (*C*-19), 168.2 ppm (*C*-1); IR (film): $\tilde{\nu}$ = 1035, 1066, 1117, 1216, 1265, 1282, 1361, 1458, 1520, 1582, 1593, 1652, 1682, 1724, 2857, 2897, 2929, 2956, 3286 cm^{-1}; HRMS (ESI): calcd for $C_{38}H_{61}NNaO_5Si_2$ [*M*+Na]$^+$: 690.39805; found: 690.39866.

Salicylihalamide A (*E*)-1: Disilylated salicylihalamide (*E*)-**36** (14.8 mg, 22.2 μmol) was treated with a solution (1.1 mL) prepared from commercially available HF•pyridine (0.5 g) in pyridine (1.25 mL) and THF (6.75 mL). After the reaction had stirred for 2 d, a further portion (0.5 mL) was added and stirring was continued for 24 h. Thereafter, the reaction was quenched by addition of buffer (pH 7, 15 mL) and the mixture was extracted with ethyl acetate (4×5 mL). The organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated in vacuo. Flash chromatography of the residue yielded salicylihalamide A (*E*)-**1** (7.3 mg, 75%) as a colorless wax: R_f = 0.44 (petroleum ether/ethyl acetate, 1:1); $[\alpha]_D$ = −37 (*c* = 0.14, MeOH); ^{1}H NMR (400 MHz, CD$_3$OD): δ = 0.86 (d, *J* = 6.7 Hz, 3H; *H*-26), 1.02 (t, *J* = 7.6 Hz, 3H; *H*-25), 1.37 (dd, *J* = 15.4, 9.2 Hz, 1H; *H*-14a), 1.71–1.80 (m, 2H; *H*-11a, *H*-14b), 1.82–1.93 (m, 1H; *H*-12), 2.23–2.33 (m, 3H; *H*-11b, *H*-24), 2.37–2.47 (m, 2H; *H*-16), 3.31–3.37 (m, 1H; *H*-8a), 3.56 (dd, *J* = 16.4, 8.1 Hz, 1H; *H*-8b), 4.12 (dd, *J* = 8.9, 3.3 Hz, 1H; *H*-13), 5.24–5.39 (m, 3H; *H*-10, *H*-15, *H*-9), 5.38 (dt, *J* = 14.3, 7.6 Hz, 1H; *H*-17), 5.69 (brd, *J* = 11.4 Hz, 1H; *H*-20), 5.83 (brdt, *J* = 10.7, 7.5 Hz, 1H; *H*-23), 6.65 (brd, *J* = 7.6 Hz, 1H; *H*-6), 6.72 (d, *J* = 8.1 Hz, 1H; *H*-4), 6.81 (brd, *J* = 14.3 Hz, 1H; *H*-18), 6.87 (dd, *J* = 12.0, 11.4 Hz, 1H; *H*-21), 7.12 (dd, *J* = 8.1, 7.6 Hz, 1H; *H*-5), 7.30 ppm (br dd, *J* = 12.0, 10.7 Hz, 1H; *H*-22); ^{13}C NMR (100 MHz, CD$_3$OD): δ = 13.5 (*C*-26), 14.4 (*C*-25), 21.5 (*C*-24), 36.5 (*C*-14), 37.6 (*C*-16), 38.5 (*C*-12), 38.8 (*C*-8), 38.9 (*C*-11), 72.0 (*C*-13), 76.0 (*C*-15), 110.4 (*C*-17), 115.3 (*C*-4), 120.3 (*C*-20), 122.4 (*C*-6), 123.1 (*C*-2), 125.3 (*C*-22), 126.2 (*C*-18), 130.7 (*C*-9), 131.6 (*C*-5), 131.7 (*C*-10), 137.8 (*C*-21), 140.6 (*C*-7), 142.6 (*C*-23), 157.1 (*C*-3), 165.8 (*C*-19), 171.0 ppm (*C*-1); IR (film): $\tilde{\nu}$ = 1032, 1064, 1120, 1215, 1248, 1294, 1367, 1464, 1506, 1647, 2846, 2871, 2929, 2961, 3292 cm^{-1}; HRMS (ESI): calcd for $C_{26}H_{33}NNaO_5$ [*M*+Na]$^+$: 462.22509; found: 462.22513.

Salicylihalamide B (*Z*)-1: Compound (*Z*)-**1** (2.0 mg, 69%) was prepared according to the procedure described above for salicylihalamide A from disilylated salicylihalamide B (*Z*)-**36** (4.4 mg, 6.6 μmol) and 0.33 mL of the HF solution: R_f = 0.49 (petroleum ether/ethyl acetate, 2:1); $[\alpha]_D$ = −69 (*c* = 0.08, MeOH); ^{1}H NMR (400 MHz, C$_6$D$_6$): δ = 0.77 (t, *J* = 7.5 Hz, 3H; *H*-25), 0.84 (d, *J* = 6.8 Hz, 3H; *H*-26), 1.22 (dd, *J* = 15.0, 8.6 Hz, 1H; *H*-14a), 1.28–1.35 (m, 1H; O*H*), 1.50 (brq, *J* = 6.5 Hz, 1H; *H*-12), 1.69–1.77 (m, 1H; *H*-11a), 1.75 (dd, *J* = 15.0, 10.7 Hz, 1H; *H*-14b), 1.83–1.91 (m, 1H; *H*-16a), 1.95 (quintd, *J* = 7.4, 0.9 Hz, 2H; *H*-24), 2.01–2.13 (m, 2H; *H*-11a, *H*-16b), 3.23–3.29 (m, 2H; *H*-8a, *H*-13), 3.53–3.60 (m, 1H; *H*-8b), 4.51 (dt, *J* = 16.0, 8.1 Hz, 1H; *H*-17), 5.08 (dt, *J* = 15.5, 6.8 Hz, 1H; *H*-9), 5.14–5.18 (m, 1H; *H*-10), 5.18–5.25 (m, 1H; *H*-15), 5.48 (d, *J* = 11.3 Hz, 1H; *H*-20), 5.63 (brdt, *J* = 10.8, 7.7 Hz, 1H; *H*-23), 6.46 (dd, *J* = 7.6, 3.1 Hz, 1H; *H*-6), 6.63 (brt, *J* = 11.6 Hz, 1H; *H*-21), 6.95–6.98 (m, 2H; *H*-4, *H*-18), 7.31 (t, *J* = 10.0 Hz, 1H; *H*-5), 7.63 (brd, *J* = 9.6 Hz, 1H; N*H*), 7.96 (brt, *J* = 11.3 Hz, 1H; *H*-22), 11.66 ppm (brs, 1H; O*H*); ^{13}C NMR (100 MHz, C$_6$D$_6$): δ = 13.8 (*C*-26), 14.0 (*C*-25), 20.8 (*C*-24), 31.4 (*C*-16), 36.1 (*C*-14), 38.0 (*C*-12), 38.4 (*C*-11), 39.4 (*C*-8), 70.9 (*C*-13), 76.1 (*C*-15), 103.2 (*C*-17), 117.2 (*C*-4), 119.5 (*C*-20), 123.7 (*C*-6), 124.9 (*C*-22), 125.4 (*C*-5), 126.8 (*C*-9), 132.8 (*C*-10), 134.7 (*C*-18), 137.4 (*C*-21), 141.9 (*C*-23), 163.0 (*C*-19), 172.1 ppm (*C*-1); IR (film): $\tilde{\nu}$ = 1033, 1063, 1117, 1213, 1293, 1364, 1464, 1505, 1589, 1651, 1701, 2852, 2870, 2927, 2962, 3357 cm; HRMS (ESI): calcd for $C_{26}H_{33}NNaO_5$ [*M*+Na]$^+$: 462.22509; found: 462.22524.

Acknowledgement

Financial support by the Deutsche Forschungsgemeinschaft (grant: Ma 1012/10-1) and the Fonds der Chemischen Industrie is gratefully acknowledged.

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Received: June 18, 2004