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Synthesis of the alkaloid tyroscherin by an aldol/Curtius strategy

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ABSTRACT

The alkaloid tyroscherin (**2**), which contains a vicinal *anti*-amino alcohol subunit was prepared from 4-hydroxyphenylpropionic acid (**5**) and *meso*-diol **9**. After desymmetrization of diol **9** and suitable protecting group manipulations, one terminus was extended via a Claisen rearrangement giving rise to enoate *ent*-**15**. The missing carbon on the other end could be incorporated using MeMgCl/CuBr·SMe_2 leading eventually to aldehyde *ent*-**22**. The acylated oxazolidinone **32** derived from acid **5** and aldehyde *ent*-**22** were combined in an aldol reaction. A subsequent Curtius rearrangement on the carboxylic group furnished the amino function of tyroscherin (**2**). In a proof of concept study the same strategy was used to prepare tyroscherin analog **28**.

1. Introduction

The β-phenylethylamine substructure is present in a range of natural and man-made molecules.[1] An unique representative of this class of compounds is tyroscherin,[2] which is a hybrid between tyrosine and a polyketide fragment. A possible biosynthetic precursor **3** is shown in Figure 1. In 2008, total synthesis studies led to the conclusion that the original published stereostructure needed revision.[3,4,5] Thus, the *syn*-amino alcohol stereochemistry actually has *anti*-configuration and the C8,C10-stereochemistry is opposite to the originally proposed configurations. The molecule was reported to inhibit the growth of cancer cells that depend on the insulin-like growth factor (IGF). The IC_{50} value for MCF-7 human breast cells containing IGF-1 (30 ng mL^{-1}) was 9.7 ng mL^{-1}. If the growth-stimulating IGF-1 is replaced by fetal bovine serum, tyroscherin had essentially no activity on these cells. Thus, a concise route to tyroscherin and possibly its stereoisomers seemed of interest. In particular derivatives thereof might allow for identification of the cellular target. The approach followed by Watanabe et al.[3,4] uses the Weinreb amide of *N*-Boc-*N*-methyl tyrosine for chain extension. The section containing the two methyl groups was later attached via a Julia olefination. We thought about forming the C2–C3 bond via an asymmetric aldol reaction followed by Curtius degradation of the carboxylic group.[6] In the following we describe the realization of this strategy.

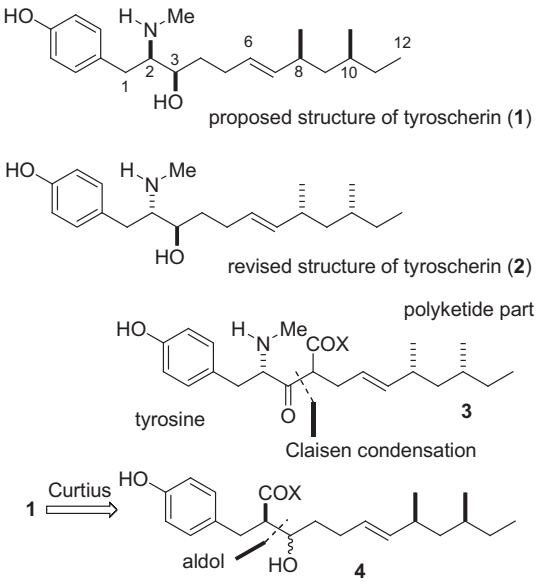

Figure 1. Structures of the proposed (**1**) and revised (**2**) tyroscherin together with the biosynthesis precursor **3** and the retrosynthetic analysis.

2. Results and discussion

The synthesis of the carboxylic acid part for the aldol reaction started with 4-hydroxyphenylpropionic acid (**5**) (Scheme 1). While the corresponding 4-triisopropylsilyl and MOM ether and could

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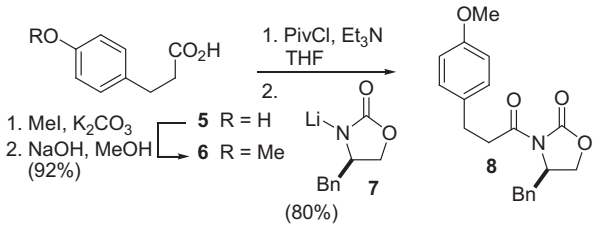
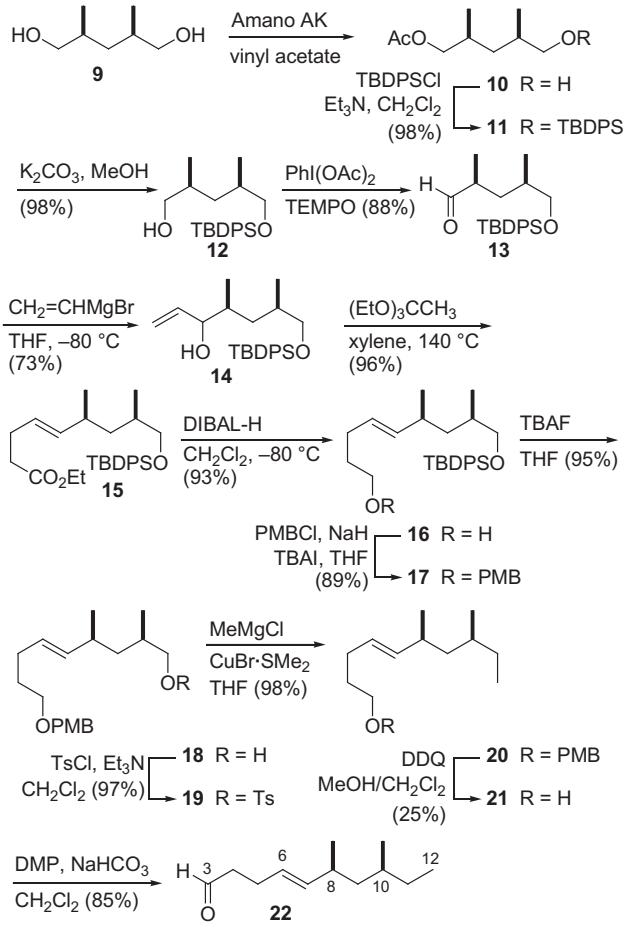
also be prepared, we faced severe problems in acylating the lithiated Evans oxazolidinone **7** via the mixed anhydride.[7] For some reason the acylation with the acid[8] **6** containing a 4-methoxyphenyl group worked nicely. The absolute configuration of the chiral auxiliary was chosen in such a way that the 3-OH group would have to be inverted at a later stage of the synthesis but the carboxyl, respectively, amino group would be correct. Thus, in one step a crucial carbon–carbon bond as well as two stereogenic centers would be formed that would open the way to tyroscherin and analogs. In addition, this strategy would allow for the preparation of oxazolidinone derivatives.[9]



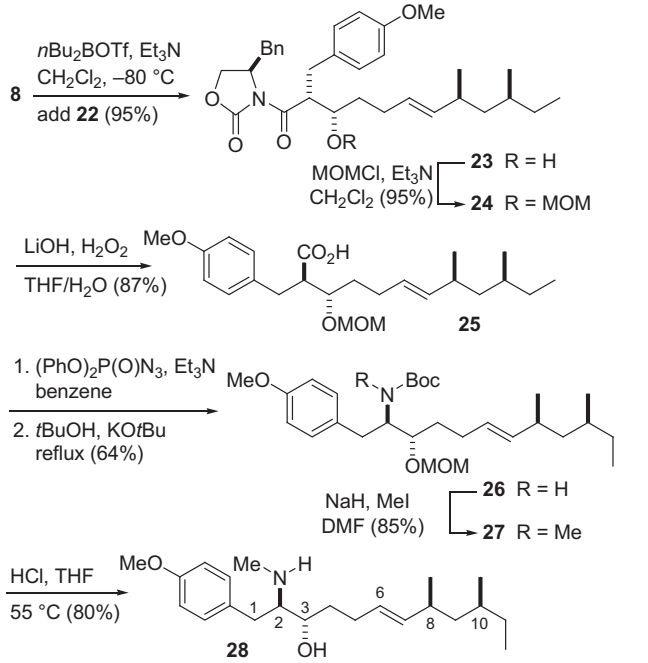
Scheme 1. Synthesis of propionyl oxazolidinone **8**.

For the synthesis of the polyketide segment we started with the known *meso*-diol **9** and relied on a desymmetrization via selective enzyme-catalyzed monoacylation (Scheme 2).[10,11] Simple protecting group manipulations led via the *tert*-butyldiphenylsilylether[12] **11** and **12** to aldehyde **13**. Reaction of aldehyde **13** with vinylmagnesium bromide furnished the vinylic alcohol **14** as a diastereomeric mixture (2:1). This was subjected to a Johnson–Claisen rearrangement[13,14] leading in almost quantitative yield to unsaturated ester **15**. Reduction of the ester **15** to alcohol **16**, protection as PMB ether **17**, cleavage of the silyl ether of compound **17** and tosylation of primary alcohol **18** provided tosylate **19**. Substitution of the tosylate with MeMgCl in presence of $CuBr \cdot SMe_2$ gave an excellent yield of the C3–C12 fragment **20**.[11,15] All these steps went with high chemical yields. In contrast, cleavage of the PMB ether in alkene **20** turned out to be problematic and only proceeded with moderate efficiency. Finally, oxidation of alcohol **21** furnished aldehyde **22**, required for the subsequent aldol reaction. An earlier introduction of the C12 methyl group was possible, but this aldehyde corresponding to **13** turned out to be rather volatile making its isolation and purification difficult.



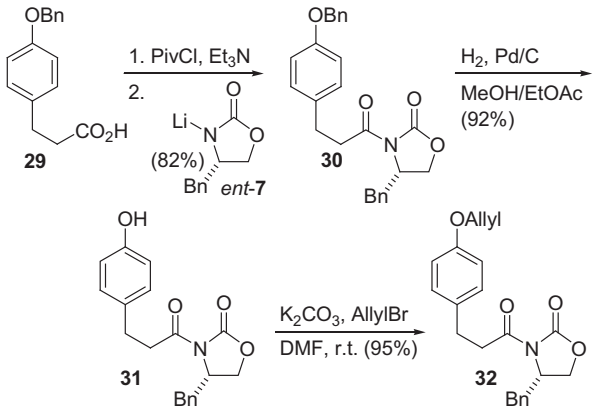
Scheme 2. Synthesis of alkenal **22**, corresponding to the C3–C12 fragment of tyroscherin.

The propionic acid derivative **8** and aldehyde **22** were combined via an Evans aldol reaction using Bu_2BOTf and Et_3N in CH_2Cl_2 at low temperature (Scheme 3).[16] The fact that we could only observe one set of signals in the ^{13}C NMR indicated the high diastereoselectivity in the aldol reaction. MOM protection of the alcohol **23** followed by saponification of the amide derivative led to acid **25**. The Curtius rearrangement was induced with diphenylphosphoryl azide[17] in presence of *tert*-butanol to provide BOC protected amine **26**. This was followed by *N*-methylation[18] and cleavage of the MOM and BOC protecting group under acidic conditions. The final cleavage of the arylmethyl ether under various conditions (BBr_3,[19] 9-I-BBN) did give the desired product according to LC–MS. However, the product was always contaminated with products resulting from addition of HX (X=Br, I) to the double bond. Therefore, another protecting group was needed. Since at this time the correct structure also became known,[3,4] the synthesis was aimed at this diastereomer. In fact, due to the C2–C3 *anti*-stereochemistry, the aldol/Curtius approach seemed even more suitable.



Scheme 3. Aldol reaction followed by Curtius-rearrangement leading to amino alcohol **26** and tyroscherin analog **28**.

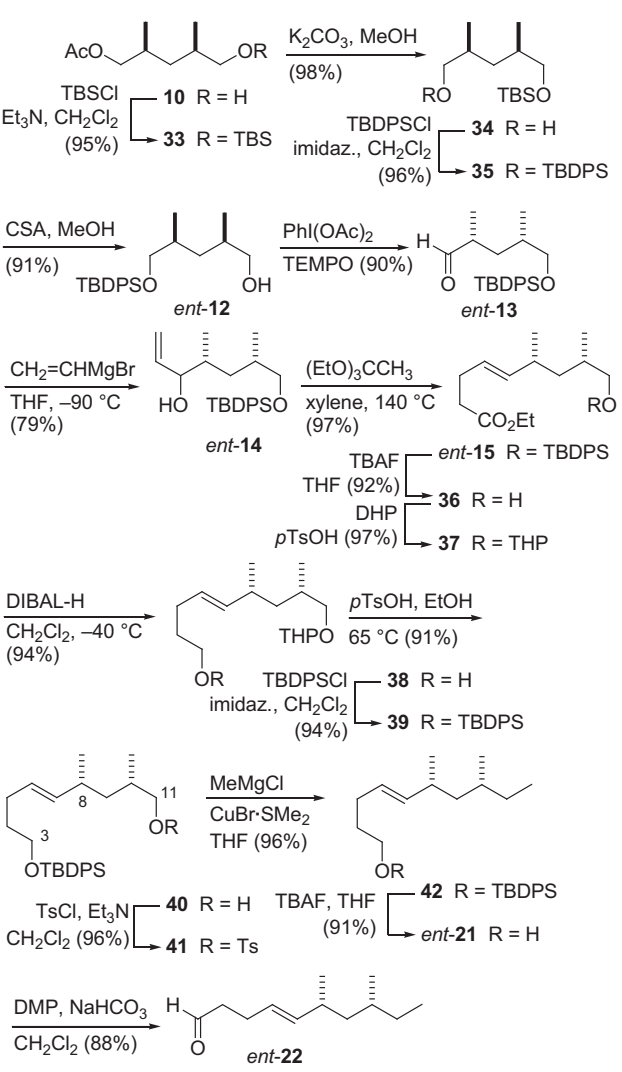
For the phenol protecting group we settled on an allyl ether. This required a small detour since the acylation of the Evans oxazolidinone only worked nicely with the methyl- or benzyl ether (Scheme 4). Thus, after acylation of lithiated oxazolidinone **7** with the mixed anhydride derived from propionic acid[20] **29**, the benzyl group was replaced with the allyl ether via hydrogenation and Williamson etherification to yield amide derivative **32**.



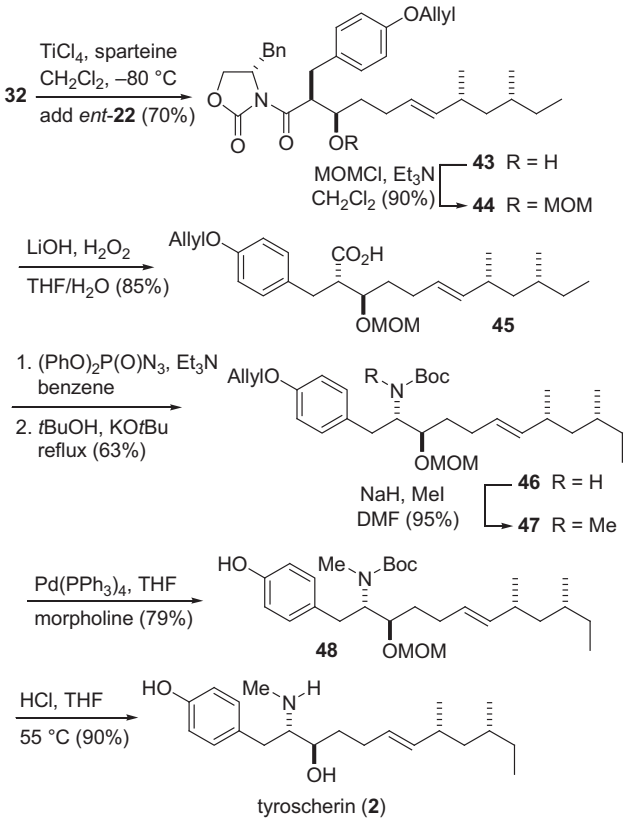
Scheme 4. Synthesis of aldol reagent **32** via the benzyl ether **30**.

In order to enter from monoacetate **10** into the enantiomeric series of the aliphatic part some protecting group shuffling was required (Scheme 5). Thus, at the stage of the bis-silyl ether **35** the TBS ether could be cleaved by acid-induced transetherification in MeOH.[21] Oxidation of the derived *ent*-**12** furnished aldehyde *ent*-**13**. As before, the vinylation-Claisen sequence gave a high yield of ester *ent*-**15**. To differentiate the two ends of the chain another combination of orthogonal protecting groups was chosen. Thus, cleavage of the silyl ether yielding hydroxyester **36**, and reprotection with the THP protecting group was followed by ester reduction and silylation. Now OH-11 (tyroscherin numbering) was set free and alcohol **40** was converted via tosylate **41** to the alkenol *ent*-**21** and alkenal *ent*-**22**.

The aldol reaction between acylated oxazolidinone derived from L-phenylalanine in presence of $TiCl_4$ and sparteine (2.5 equiv) gave a 70% yield of hydroxy acid derivative **43**.[22] With the classical boron enolate (Bu_2BOTf, Et_3N, CH_2Cl_2) only a low yield could be realized for this aldol reaction. The four-step sequence consisting of alcohol protection to MOM ether **44**, removal of the chiral auxiliary yielding acid **45**, Curtius rearrangement, and *N*-methylation of the carbamate **46** delivered the tyroscherin precursor **47**. The global deprotection required a Pd-catalyzed deallylation and acid hydrolysis of the BOC and MOM groups. The optical rotation {$[\alpha]_D^{20}$ −19.0 (*c* 0.35, MeOH)} matched pretty well with the reported one[2] {$[\alpha]_D^{24}$ −21.0 (*c* 0.35, MeOH)}. According to the ^1H NMR the synthetic material corresponds to the natural compound. However, we could not obtain the sharp resolution as reported by Watanabe et al.[3,4] The same was the case for the trifluoroacetate salt. We made this salt because it has been reported that with an alkaloid this can lead to better resolved spectra.[23] The ^{13}C NMR spectrum showed the correct chemical shifts (Scheme 6).



Scheme 5. Synthesis of aldehyde *ent*-**22** from monoacetate **10**.



Scheme 6. Completion of the total synthesis of tyroscherin (**2**).

3. Conclusion

In conclusion, we accomplished the synthesis of the alkaloid tyroscherin and a diastereomer by a novel strategy. In the key step, the C2–C3 bond was created by an aldol reaction. The carboxylic function in the aldol product served as precursor for the 2-amino group, obtained via Curtius degradation.

4. Experimental section

4.1. General

*4.1.1. 3-[4-(Benzyloxy)phenyl]propanoic acid (**29**).* A mixture of 3-(4′-hydroxyphenyl)propionic acid (4.99 g, 30 mmol), benzyl chloride (13.9 mL, 120 mmol), KI (19.92 g, 120 mmol), and K_2CO_3 (16.59 g, 120 mmol) in acetone (70 mL) was refluxed for 36 h. After cooling, water was added and the mixture extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude ester was taken up in H_2O/20% NaOH (100 mL, 1:1) and the mixture refluxed for 2 h. After cooling, CH_2Cl_2 (100 mL) was added, the layers were separated and the CH_2Cl_2 layer washed with 5% NaOH (2×40 mL). The combined water layers were acidified with concd HCl and extracted with CH_2Cl_2 (3×80 mL). These combined CH_2Cl_2 layers were dried over $MgSO_4$, filtered, and concentrated in vacuo yielding acid **29** (6.30 g, 82%) as a colorless solid. R_f (petroleum ether/ethyl acetate, 1:1) 0.15; δ_H (400 MHz, $CDCl_3$) 2.64 (t, J=7.8 Hz, 2H, 2-H), 2.90 (t, J=7.8 Hz, 2H, 3-H), 5.03 (s, 2H, CH_2 aryl), 6.50 (d, J=8.7 Hz, 2H, aryl), 7.12 (d, J=8.7 Hz, 2H, aryl), 7.29–7.33 (m, 1H, aryl), 7.35–7.43 (m, 4H, aryl); δ_C (100 MHz, $CDCl_3$) 29.8 (C-3), 35.7 (C-2), 70.1 (CH_2 aryl), 114.9 (CH aryl), 127.5, 127.9, 128.6 (CH aryl), 129.3 (CH aryl), 132.5 (C aryl), 137.1 (C aryl), 157.4 (CO aryl), 178.2 (C-1).

*4.1.2. (4S)-4-Benzyl-3-{3-[4-(benzyloxy)phenyl]propanoyl}-1,3-oxazolidin-2-one (**30**).* To a solution of acid **29** (2.0 g, 7.80 mmol) and Et_3N (3.3 mL, 23.4 mmol) in THF (60 mL), was added pivaloyl chloride (1.0 mL, 8.19 mmol) at −20 °C followed by stirring of the mixture at −20 °C for 30 min and 30 min at room temperature. In a separate flask the anion **7** of the oxazolidinone was prepared by dropwise addition of ^{n}BuLi (3.28 mL, 8.19 mmol, 2.5 M in hexane) to a solution of the auxiliary (1.38 g, 7.80 mmol) in THF (8 mL) at −80 °C followed by stirring for 15 min at this temperature. This solution of anion **7** was added via cannula to the cooled (−80 °C) solution of the mixed anhydride. After complete addition, the stirred mixture was allowed to reach room temperature. The mixture was treated with satd $NaHCO_3$ solution and extracted with ethyl acetate (3×60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was recrystallized from ethyl acetate to yield amide derivative **30** (2.65 g, 82%) as colorless needles. Mp 106 °C; R_f (petroleum ether/ethyl acetate, 2:1) 0.23; $[\alpha]_D^{20}$ +48.0 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.74 (dd, J=13.4, 9.5 Hz, 1H, $PhCH_2$), 2.94–2.98 (m, 2H, 3′-H), 3.16–3.32 (m, 3H, 2′-H, $PhCH_2$), 4.14–4.16 (m, 2H, 4-H), 4.62–4.68 (m, 1H, 5-H), 5.04 (s, 2H, $PhCH_2O$), 6.91 (d, J=8.7 Hz, 2H, aryl), 7.16–7.43 (m, 7H, aryl); δ_C (100 MHz, $CDCl_3$) 29.4 (C-3′), 37.3 ($PhCH_2$), 37.8 (C-2′), 55.1 (C-4), 66.2 ($PhCH_2O$), 70.0 (C-5), 114.8 (CH aryl), 127.3 (CH aryl), 127.4 (CH aryl), 127.9 (CH aryl), 128.5 (CH aryl), 128.9 (CH aryl), 129.4 (CH aryl), 129.5 (CH aryl), 132.8 (C aryl), 135.2 (C aryl), 137.1 (C aryl), 153.4 (C-2), 157.4 (CO aryl), 172.5 (C-1′).

*4.1.3. (4S)-4-Benzyl-3-[3-(4-hydroxyphenyl)propanoyl]-1,3-oxazolidin-2-one (**31**).* A solution of benzyl ether **30** (1.75 g, 4.21 mmol) in MeOH/ethyl acetate (80 mL, 1:1) containing Pd/C (200 mg) was hydrogenated for 1.5 h at room temperature. The catalyst was filtered off, and the filtrate was concentrated in vacuo. The crude product was recrystallized from petroleum ether/ethyl acetate, 1:8 to give phenol **31** (1.26 g, 92%) as a colorless solid. R_f (petroleum ether/ethyl acetate, 2:1) 0.32; $[\alpha]_D^{20}$ −61.1 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.74 (dd, J=13.4, 9.5 Hz, 1H, $PhCH_2$), 2.92–2.97 (m, 2H, 3′-H), 3.15–3.31 (m, 3H, 2′-H, $PhCH_2$), 4.14–4.17 (m, 2H, 4-H), 4.62–4.68 (m, 1H, 5-H), 6.75 (d, J=8.7 Hz, 2H, aryl), 7.11–7.33 (m, 7H, aryl); δ_C (100 MHz, $CDCl_3$) 29.5 (C-3′), 37.4 ($PhCH_2$), 37.8 (C-2′), 55.1 (C-4), 66.2 (C-5), 115.3 (CH aryl), 127.4 (CH aryl), 129.0 (CH aryl), 129.4 (CH aryl), 129.7 (CH aryl), 132.5 (C aryl), 135.2 (C aryl), 153.5 (C-2), 154.0 (CO aryl), 172.5 (C-1′).

*4.1.4. (4S)-3-{3-[4-(Allyloxy)phenyl]propanoyl}-4-benzyl-1,3-oxazolidin-2-one (**32**).* A mixture of phenol **31** (152 mg, 0.467 mmol), K_2CO_3 (162 mg, 1.168 mmol), and allyl bromide (82 μL, 0.934 mmol) in DMF (2 mL) was stirred for 10 h at room temperature. Then water was added and the mixture extracted with ethyl acetate (3×25 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 1:1) provided allyl ether **32** (162 mg, 95%) as an amorphous solid. R_f (petroleum ether/ethyl acetate, 2:1) 0.56; $[\alpha]_D^{20}$ +44.3 (c 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 2.74 (dd, J=13.5, 9.7 Hz, 1H, $PhCH_2$), 2.96 (ddd, J=7.7, 2.8 Hz, 2H, 3′-H), 3.16–3.32 (m, 3H, 2′-H, $PhCH_2$), 4.14–4.17 (m, 2H, 4-H), 4.50 (dt, J=5.3, 1.4 Hz, 2H, $OCH_2CH{=}CH_2$), 4.65 (ddd, J=13.0, 6.8, 3.6 Hz, 1H, 5-H), 5.26 (dd, J=10.6, 1.4 Hz, 1H, $CH{=}CH_2$), 5.39 (dd, J=17.2, 1.7 Hz, 1H, $CH{=}CH_2$), 5.99–6.09 (m, 1H, $CH{=}CH_2$), 6.85 (d, J=8.7 Hz, 2H, aryl), 7.15–7.18 (m, 4H, aryl), 7.25–7.33 (m, 4H, aryl); δ_C (100 MHz, $CDCl_3$) 29.4 (C-3′), 37.3 ($PhCH_2$), 37.8 (C-2′), 55.1 (C-5), 66.1 (C-4), 68.8 ($OCH_2CH{=}CH_2$), 114.7 (CH aryl), 117.5 ($CH{=}CH_2$), 127.3 (CH aryl), 128.9 (CH aryl), 129.5 (CH aryl), 132.7 ($CH{=}CH_2$), 133.4 (C aryl), 135.2 (C aryl), 153.4 (C-2), 157.1 (CO aryl), 172.5 (C-1′); HRMS (ESI): $[M+Na]^+$ calcd for $C_{22}H_{23}NO_4Na$ 388.15248, found 388.15256.

*4.1.5. (2S,4R)-5-{[tert-Butyl(dimethyl)silyl]oxy}-2,4-dimethylpentyl acetate (**33**).* To a solution of alcohol **10** (1.5 g, 8.6 mmol) and imidazole (940 mg, 13.8 mmol) in CH_2Cl_2 (20 mL) was added TBSCl (1.56 g, 10.3 mmol) at 0 °C. The cooling bath was removed and the mixture stirred at room temperature for 30 min. The mixture was treated with satd NH_4Cl solution and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give silyl ether **33** (2.36, 95%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 25:1) 0.45; $[\alpha]_D^{20}$ +23.0 (c 1.0, CHCl3); δ_H (400 MHz, $CDCl_3$) 0.01 (s, 6H, $(CH_3)_2Si$), 0.87 (s, 9H, ^{t}Bu), 0.88 (d, J=6.6 Hz, 3H, 4-CH_3), 0.90 (m, 1H, 3-H), 0.92 (d, J=6.6 Hz, 3H, 2-CH_3), 1.44 (m, 1H, 3-H), 1.67 (m, 4-H), 1.88 (m, 1H, 2-H), 2.02 (s, 3H, H_3CCO_2), 3.34 (dd, J=9.6, 6.3 Hz, 1H, 5-H), 3.41 (dd, J=9.6, 5.6 Hz, 1H, 5-H), 3.80 (dd, J=10.9, 6.9 Hz, 1H, 1-H), 3.94 (dd, J=10.9, 5.3 Hz, 1H, 1-H); δ_C (100 MHz, $CDCl_3$) −5.4 ($(CH_3)_2Si$), 17.4 (4-CH_3), 17.8 (2-CH_3), 18.2 ($C(CH_3)_3$), 20.9 (CH_3CO_2), 25.9 ($C(CH_3)_3$), 30.0 (C-2), 33.0 (C-4), 37.4 (C-3), 68.0 (C-5), 69.3 (C-1), 171.2 (CO).

*4.1.6. (2S,4R)-5-{[tert-Butyl(dimethyl)silyl]oxy}-2,4-dimethylpentan-1-ol (**34**).* A mixture of acetate **33** (7.8 g, 27.09 mmol) and K_2CO_3 (4.88 g, 35.2 mmol) in MeOH (40 mL) was stirred for 2 h at room temperature. The solids were filtered off and the filtrate concentrated in vacuo. The residue was taken up in CH_2Cl_2 (150 mL) and extracted with water (3×80 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give alcohol **34** (6.61 g, 98%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 9:1) 0.3; $[\alpha]_D^{20}$ −2.0 (c 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.03 (s, 6H), 0.87–0.92 (m, 13H), 0.93 (d, J=6.6 Hz, 3H), 1.43 (dt, J=13.6, 6.8 Hz, 1H), 1.61 (br s, 1H), 1.71 (m, 2H), 3.35–3.55 (m, 4H); δ_C (100 MHz, $CDCl_3$) −5.4 ($(CH_3)_2SiC$), 17.7 (4-CH_3), 17.8 (2-CH_3), 18.3 ($C(CH_3)_3$), 25.9 ($C(CH_3)_3$), 33.2 (C-2), 33.3 (C-4), 37.3 (C-3), 68.2 (C-1), 68.3 (C-5).

*4.1.7. (2R,4S)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2,4-dimethylpentan-1-ol (ent-**12**).* To a solution of alcohol **34** (5.28 g, 21.44 mmol), imidazole (2.0 g, 30.0 mmol), and DMAP (187 mg, 1.53 mmol) in CH_2Cl_2 (20 mL) was added TBDPSCl (6.76 g, 24.66 mmol) at 0 °C.

The cooling bath was removed and the mixture stirred at room temperature for 45 min. The mixture was treated with satd NH_4Cl solution and extracted with CH_2Cl_2 (3×65 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 9:1) to give disilyl ether **35** (10.0 g, 96%) as a slightly yellow oil.

A solution of disilyl ether **35** (10.0 g, 20.6 mmol) and CSA (170 mg, 0.732 mmol) in MeOH (35 mL) was stirred for 2.5 h at room temperature. Then Et_3N (1 mL) was added, the solvent evaporated in vacuo and the residue taken up in CH_2Cl_2 (90 mL). The CH_2Cl_2 solution was washed with satd NH_4Cl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc, 5:1) to give silyl ether *ent*-**12** (6.94 g, 91%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 5:1) 0.43; $[\alpha]_D^{20}$ +1.7 (*c* 0.2, $CHCl_3$); Ref. [21] $[\alpha]_D^{20}$ +1.8 (*c* 0.23, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.88 (d, *J*=6.6 Hz, 3H, 4-CH_3), 0.95 (d, *J*=6.6 Hz, 3H, 2-CH_3), 1.24–1.27 (m, 1H, 3-H), 1.42–1.48 (m, 1H, 3-H), 1.59–1.67 (m, 1H, 4-H), 1.69–1.77 (m, 1H, 2-H), 3.31–3.37 (m, 1H, 1-H), 3.40–3.53 (m, 3H, 1-H, 5-H), 7.35–7.43 (m, 6H, Phenyl), 7.65–7.67 (m, 4H, Phenyl); δ_C (100 MHz, $CDCl_3$) 17.4 (4-CH_3), 17.9 (2-CH_3), 19.3 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 33.1 (C-2), 33.2 (C-4), 37.1 (C-3), 68.3 (C-1), 68.7 (C-5), 127.6 (CH aryl), 129.5 (CH aryl), 134.0 (C aryl), 135.6 (C aryl).

*4.1.8. (2R,4S)-5-{[tert-Butyl(diphenyl)silyl]oxy}-2,4-dimethylpentanal (ent-**13**).* To a solution of alcohol *ent*-**12** (8.31 g, 22.0 mmol) in CH_2Cl_2 (90 mL) were added $PhI(OAc)_2$ (10.6 g, 33.0 mmol) and TEMPO (348 mg, 2.2 mmol) followed by stirring of the mixture for 2 h at room temperature. This was followed by the addition of 10% aqueous $Na_2S_2O_3$ solution (40 mL) and stirring for 15 min. The mixture was extracted with CH_2Cl_2 (3×110 mL). The combined organic layers were washed with satd $NaHCO_3$ solution, satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 60:1) to give aldehyde *ent*-**13** (7.29 g, 90%) as a slightly orange oil. R_f (petroleum ether/ethyl acetate, 60:1) 0.24; $[\alpha]_D^{20}$ −6.6 (*c* 0.4, $CHCl_3$); Ref. [21] $[\alpha]_D^{20}$ −6.3 (*c* 0.4, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.77 (d, *J*=6.6 Hz, 3H, 4-CH_3), 0.88 (d, *J*=3.3 Hz, 3H, 2-CH_3), 0.89 (s, 9H, ^{t}Bu), 0.95 (dd, *J*=19.9, 7.3 Hz, 1H, 5-H), 1.52–1.61 (m, 1H, 4-H), 1.68–1.76 (m, 1H, 5-H), 2.17–2.26 (m, 1H, 2-H), 3.31 (ddd, *J*=12.0, 10.1, 5.9 Hz, 2H, 3-H), 7.18–7.24 (m, 6H, phenyl), 7.47–7.49 (m, 4H, phenyl), 9.37 (d, *J*=2.3 Hz, 1H, 1-H); δ_C (100 MHz, $CDCl_3$) 14.1 (2-CH_3), 17.2 (4-CH_3), 19.3 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 33.3 (C-3), 34.5 (C-4), 44.0 (C-2), 68.4 (C-5), 127.6 (CH phenyl), 129.6 (CH phenyl), 133.8 (C phenyl), 135.6 (CH phenyl), 205.3 (C-1).

*4.1.9. (4R,6S)-7-{[tert-Butyl(diphenyl)silyl]oxy}-4,6-dimethylhept-1-en-3-ol (ent-**14**).* To a solution of aldehyde *ent*-**13** (6.77 g, 18.4 mmol) in THF (90 mL) was added dropwise vinylmagnesium bromide (27.6 mL, 1 M in THF) at −90 °C. The stirred mixture was allowed to warm to room temperature within 1 h. Then satd NH_4Cl solution was added and the mixture extracted with Et_2O (3×120 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 12:1) gave vinyl alcohol *ent*-**14** (5.76 g, 79%) as a colorless oil (roughly 2:1 mixture of C-3 diastereomers). R_f (petroleum ether/ethyl acetate, 12:1) 0.31; δ_H (400 MHz, $CDCl_3$) 0.83 (d, *J*=6.6 Hz, 3H, 6-CH_3), 0.86–0.93 (m, 1H, 5-H), 0.96 (m, 3H, 4-CH_3), 1.05 (s, 9H, ^{t}Bu), 1.50–1.57 (m, 1H, 6-H), 1.58–1.66 (m, 1H, 5-H), 1.72–1.80 (m, 1H, 4-H), 3.40–3.55 (m, 2H, 7-H), 3.92–3.95 (m, 1H, 3-H), 5.11–5.15 (m, 1H, 1-H), 5.18–5.23 (m, 1H, 1-H), 5.77–5.87 (m, 1H, 2-H), 7.35–7.44 (m, 6H, phenyl), 7.66 (dd, *J*=7.8, 1.7 Hz, 4H, phenyl); δ_C (100 MHz, $CDCl_3$) 14.6 (6-CH_3), 18.2 (4-CH_3), 19.3 ($C(CH_3)_3$), 26.9 ($C(CH_3)_3$), 33.1 (C-9), 35.9 (C-4), 36.7 (C-6), 68.4 (C-7), 76.3 (C-3), 115.0 (C-1), 127.6 (CH phenyl), 129.5 (CH phenyl), 134.0 (C phenyl), 135.6 (CH phenyl), 139.9 (C-2); HRMS (ESI): $[M+Na]^+$ calcd for $C_{25}H_{36}O_2SiNa$ 419.23768, found 419.23763.

*4.1.10. Ethyl (4E,6R,8S)-9-{[tert-butyl(diphenyl)silyl]oxy}-6,8-dimethylnon-4-enoate (ent-**15**).* A mixture of allylalcohol *ent*-**14** (6.10 g, 15.38 mmol), triethylorthoacetate (8.7 mL, 46.14 mmol), and propionic acid (50 μL) in xylene (50 mL) was refluxed for 5 h. After cooling the solvent was removed in vacuo and the residue purified by flash chromatography (petroleum ether/EtOAc, 25:1) to give the enoate *ent*-**15** (6.96 g, 97%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 25:1) 0.22; $[\alpha]_D^{20}$ −6.65 (*c* 2.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.88 (d, *J*=6.6 Hz, 3H, 8-CH_3), 0.92 (d, *J*=6.9 Hz, 3H, 6-CH_3), 0.98–1.03 (m, 1H, 7-H), 1.05 (s, 9H, ^{t}Bu), 1.24 (t, *J*=7.1 Hz, 3H, CH_3CH_2O), 1.32–1.39 (m, 1H, 7-H), 1.59–1.70 (m, 1H, 8-H), 2.09–2.19 (m, 1H, 6-H), 2.26–2.36 (m, 4H, 2-H, 3-H), 3.39–3.50 (m, 2H, 9-H), 4.12 (q, *J*=7.1 Hz, 2H, CH_3CH_2O), 5.21–5.26 (m, 1H, 5-H), 5.32–5.39 (m, 1H, 4-H), 7.35–7.43 (m, 6H, phenyl), 7.66 (dd, *J*=7.8, 1.7 Hz, 4H, phenyl); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3CH_2O), 16.7 (8-CH_3), 19.3 ($C(CH_3)_3$), 21.8 (6-CH_3), 26.9 ($C(CH_3)_3$), 27.9 (C-3), 33.4 (C-2), 34.2 (C-8), 34.5 (C-6), 40.7 (C-7), 60.2 (CH_3CH_2O), 69.3 (C-9), 126.4 (C-4), 127.5 (CH phenyl), 129.5 (CH phenyl), 134.1 (C phenyl), 135.6 (CH phenyl), 137.5 (C-5), 173.2 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{29}H_{42}O_3SiNa$ 489.28009, found 489.27981.

*4.1.11. Ethyl (4E,6R,8S)-9-hydroxy-6,8-dimethylnon-4-enoate (**36**).* To a solution of ester *ent*-**15** (101 mg, 0.22 mmol) in THF (3 mL) was added TBAF (102 mg, 0.33 mmol) and the mixture stirred for 3 h at room temperature. Then satd NH_4Cl solution was added and the mixture extracted with Et_2O (3×40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 3:1) to give hydroxyester **36** (45 mg, 92%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 2:1) 0.5; $[\alpha]_D^{20}$ −23.8 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.86 (d, *J*=6.6 Hz, 3H, 8-CH_3), 0.94 (d, *J*=6.9 Hz, 3H, 6-CH_3), 0.98–1.04 (m, 1H, 7-H), 1.24 (t, *J*=7.1 Hz, 3H, CH_3CH_2O), 1.28–1.34 (m, 1H, 7-H), 1.55–1.63 (m, 1H, 8-H), 2.11–2.20 (m, 1H, 6-H), 2.26–2.36 (m, 4H, 2-H, 3-H), 3.36–3.45 (m, 2H, 9-H), 4.10 (q, *J*=7.1 Hz, 2H, CH_3CH_2O), 5.20–5.26 (m, 1H, 5-H), 5.33–5.40 (m, 1H, 4-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3CH_2O), 16.3 (8-CH_3), 21.9 (6-CH_3), 27.9 (C-3), 33.5 (C-8), 34.4 (C-2), 34.5 (C-6), 40.7 (C-7), 60.3 (CH_3CH_2O), 68.7 (C-9), 126.7 (C-4), 137.3 (C-5), 173.3 (C-1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{13}H_{24}O_3Na$ 251.16231, found 251.16207.

*4.1.12. Ethyl (4E,6R,8S)-6,8-dimethyl-9-(tetrahydro-2H-pyran-2-yloxy)non-4-enoate (**37**).* A solution of hydroxyester **36** (1.65 g, 7.23 mmol), 3,4-dihydropyran (1.0 mL, 10.8 mmol), and *p*TsOH (181 mg, 0.72 mmol) in CH_2Cl_2 (12 mL) was stirred for 3 h at room temperature. Then satd $NaHCO_3$ solution was added and the mixture extracted with CH_2Cl_2 (3×60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 12:1) to give THP ether **37** (2.19 g, 97%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 12:1) 0.4; $[\alpha]_D^{20}$ −6.5 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.87 (dd, *J*=8.5, 6.7 Hz, 3H, 8-CH_3), 0.93 (d, *J*=6.6 Hz, 3H, 6-CH_3), 0.97–1.04 (m, 1H, 7-H), 1.23 (t, *J*=7.1 Hz, 3H, CH_3CH_2O), 1.28–1.37 (m, 1H, 7-H), 1.48–1.60 (m, 4H, 4′-H, 5′-H), 1.65–1.73 (m, 2H, 3′-H), 1.78–1.85 (m, 1H, 8-H), 2.12–2.23 (m, 1H, 6-H), 2.25–2.35 (m, 4H, 2-H, 3-H), 3.07–3.20 (m, 1H, 9-H), 3.42–3.56 (m, 2H, 6′-H), 3.80–3.86 (m, 1H, 9-H), 4.10 (q, *J*=7.1 Hz, 2H, CH_3CH_2O), 4.51–4.55 (m, 1H, 2′-H), 5.21–5.28 (m, 1H, 5-H), 5.32–5.39 (m, 1H, 4-H); δ_C (100 MHz, $CDCl_3$) 14.2 (CH_3CH_2O), 16.8, 16.9 (8-CH_3), 19.5, 19.6 (C-4′), 21.8 (6-CH_3), 25.5 (C-5′), 27.9 (C-3), 30.7 (C-3′), 31.0, 31.1 (C-8), 34.2 (C-2), 34.5 (C-6), 41.0, 41.1 (C-7), 60.2 (CH_3CH_2O), 62.0, 62.2 (C-6′), 73.3, 73.5 (C-9), 98.7, 99.0 (C-2′), 126.5 (C-4), 137.3 (C-5), 173.2 (C-

1); HRMS (ESI): $[M+Na]^+$ calcd for $C_{18}H_{32}O_4Na$ 335.21983, found 335.21933.

*4.1.13. (4E,6R,8S)-6,8-Dimethyl-9-(tetrahydro-2H-pyran-2-yloxy)non-4-en-1-ol (**38**).* To a solution of ester **37** (2.18 g, 7.0 mmol) in abs Et_2O (18 mL) was added DIBAL–H (21 mL, 1 M in hexane) dropwise at −40 °C. After complete addition, stirring was continued for 40 min at −40 °C and 4 h at 0 °C. The mixture was treated with satd $NaHCO_3$ solution and extracted with Et_2O (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 2:1) to give alcohol **38** (1.77 g, 94%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 2:1) 0.4; $[\alpha]_D^{20}$ −8.3 (*c* 2.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.88 (t, *J*=6.7 Hz, 3H, 8-CH_3), 0.94 (d, *J*=6.6 Hz, 3H, 6-CH_3), 0.98–1.05 (m, 1H, 7-H), 1.44–1.58 (m, 4H, 4′-H, 5′-H), 1.59–1.63 (m, 2H, 2-H), 1.65–1.75 (m, 2H, 3′-H), 1.77–1.84 (m, 1H, 8-H), 2.05 (q, *J*=7.1 Hz, 2H, 3-H), 2.13–2.23 (m, 1H, 6-H), 3.08–3.21 (m, 1H, 9-H), 3.43–3.58 (m, 2H, 6′-H), 3.63 (q, *J*=5.8, 2H, 1-H) 3.82–3.86 (m, 1H, 9-H), 4.52–4.55 (m, 1H, 2′-H), 5.20–5.26 (m, 1H, 5-H), 5.33–5.40 (m, 1H, 4-H); δ_C (100 MHz, $CDCl_3$) 16.9 (8-CH_3), 19.5, 19.6 (C-4′), 21.9, 22.0 (6-CH_3), 25.5 (C-5′), 28.8 (C-3), 30.7 (C-3′), 31.0, 31.1 (C-2), 32.4 (C-8), 34.3, 34.4 (C-6), 41.1 (C-7), 62.0 (C-1), 62.3, 62.4 (C-6′), 73.3, 73.5 (C-9), 98.7, 99.1 (C-1′), 127.9 (C-4), 136.8 (C-5); HRMS (ESI): $[M+Na]^+$ calcd for $C_{16}H_{30}O_3Na$ 293.205918, found 293.20575.

*4.1.14. tert-Butyl{[(4E,6R,8S)-6,8-dimethyl-9-(tetrahydro-2H-pyran-2-yloxy)non-4-enyl]oxy}diphenylsilane (**39**).* To a solution of alcohol **38** (1.82 g, 6.73 mmol), imidazole (642 mg, 9.4 mmol), and DMAP (83 mg, 0.67 mmol) in CH_2Cl_2 (12 mL) was added TBDPSCl (2.04 g, 7.40 mmol) at 0 °C. The cooling bath was removed and the mixture stirred at room temperature for 1 h. The mixture was treated with satd NH_4Cl solution and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (petroleum ether/EtOAc, 15:1) to give silyl ether **39** (3.22 g, 94%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 15:1) 0.43; $[\alpha]_D^{20}$ −5.2 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.88 (dd, *J*=9.7, 6.6 Hz, 3H, 8-CH_3), 0.93 (d, *J*=6.0 Hz, 3H, 6-CH_3), 0.96–1.02 (m, 1H, 7-H), 1.04 (s, 9H, ^{t}Bu), 1.25–1.37 (m, 1H, 7-H), 1.49–1.65 (m, 6H, 2-H, 4′-H, 5′-H), 1.66–1.85 (m, 3H, 8-H, 2′-H) 2.06 (q, *J*=7.0 Hz, 2H, 3-H), 2.13–2.20 (m, 1H, 6-H), 3.08–3.21 (m, 1H, 9-H), 3.45–3.50 (m, 2H, 6′-H), 3.65 (t, *J*=6.5 Hz, 2H, 1-H), 3.82–3.87 (m, 1H, 9-H), 4.52–4.56 (m, 1H, 1′-H), 5.16–5.22 (m, 1H, 5-H), 5.30–5.37 (m, 1H, 4-H), 7.35–7.43 (m, 6H, aryl), 7.63 (dd, *J*=7.6, 1.5 Hz, 4H, aryl); δ_C (100 MHz, $CDCl_3$) 16.9, 17.0 (8-CH_3), 19.2 (*C*(CH_3)$_3$), 19.5, 19.7 (C-4′), 21.9, 22.0 (6-CH_3), 25.5 (C-5′), 26.9 (C(*C*H_3)$_3$), 28.8 (C-2), 30.7 (C-2′), 31.7 (C-8), 32.6 (C-3), 34.2, 34.3 (C-6), 41.2 (C-7), 62.0, 62.2 (C-6′), 62.3, 62,4 (C-1), 73.3, 73.5 (C-9), 98.7, 99.1 (C-1′), 127.6 (CH aryl), 128.2 (CH aryl), 129.5 (CH aryl), 134.1 (C aryl), 135.6 (CH aryl), 136.3, 136.4 (C-5); HRMS (ESI): $[M+Na]^+$ calcd for $C_{32}H_{48}O_3SiNa$ 531.32704, found 531.32689.

*4.1.15. (2S,4R,5E)-9-{[tert-Butyl(diphenyl)silyl]oxy}-2,4-dimethylnon-5-en-1-ol (**40**).* A solution of THP ether **39** (3.11 g, 6.12 mmol) and PPTS (77 mg, 0.31 mmol) in EtOH (20 mL) was stirred for 8 h at 55 °C. Then the solvent was removed in vacuo and the residue subjected to flash chromatography (petroleum ether/EtOAc, 9:1) to give alcohol **40** (2.36 g, 91%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 4:1) 0.47; $[\alpha]_D^{20}$ −14.7 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.86 (d, *J*=6.6 Hz, 3H, 2-CH_3), 0.95 (d, *J*=6.6 Hz, 3H, 4-CH_3), 0.97–1.03 (m, 1H, 3-H), 1.05 (s, 9H, ^{t}Bu), 1.27–1.33 (m, 1H, 3-H), 1.56–1.66 (m, 3H, 2-H, 2-H), 2.07 (q, *J*=7.1 Hz, 2H, 7-H), 2.12–2.21 (m, 1H, 4-H), 3.34–3.47 (m, 2H, 1-H), 3.66 (t, *J*=6.4 Hz, 2H, 9-H), 5.15–5.21 (m, 1H, 5-H), 5.31–5.38 (m, 1H, 6-H), 7.35–7.44 (m, 6H, aryl), 7.66–7.68 (m, 4H, aryl); δ_C (100 MHz, $CDCl_3$) 16.3 (2-CH_3), 19.2 (*C*(CH_3)$_3$), 22.1 (4-CH_3), 26.9 (C(*C*H_3)$_3$), 28.7 (C-8), 32.5 (C-7), 33.5 (C-2), 34.3 (C-4), 46.7 (C-3), 63.3 (C-9), 68.8 (C-1), 127.6 (CH aryl), 128.4 (C-6), 129.5 (CH aryl), 134.1 (C aryl), 135.5 (CH aryl), 136.2 (C-5); HRMS (ESI): $[M+Na]^+$ calcd for $C_{27}H_{40}O_2SiNa$ 447.26952, found 447.26935.

*4.1.16. (2S,4R,5E)-9-{[tert-Butyl(diphenyl)silyl]oxy}-2,4-dimethylnon-5-enyl 4-methylbenzenesulfonate (**41**).* To a solution of alcohol **40** (2.28 g, 5.37 mmol) in CH_2Cl_2 (15 mL) were added Et_3N (1.74 mL, 12.35 mmol), DMAP (132 mg, 1.07 mmol), and tosyl chloride (1.20 g, 6.15 mmol). The resulting mixture was stirred for 2 h at room temperature before it was treated with satd NH_4Cl solution and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with satd NaCl solution, dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave tosylate **41** (3.04 g, 96%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 9:1) 0.41; $[\alpha]_D^{20}$ −3.8 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.82 (d, *J*=6.9 Hz, 3H, 2-CH_3), 0.89 (d, *J*=6.6 Hz, 3H, 4-CH_3), 0.96–1.02 (m, 1H, 3-H), 1.04 (s, 9H, ^{t}Bu), 1.16–1.23 (m, 1H, 3-H), 1.59 (ddd, *J*=14.1, 6.9, 6.7 Hz, 2H, 8-H), 1.72–1.80 (m, 1H, 2-H), 2.01–2.10 (m, 3H, 4-H, 7-H), 2.43 (s, 3H, aryl CH_3), 3.64 (t, *J*=6.4 Hz, 2H, 9-H), 3.75 (dd, *J*=9.4, 6.4 Hz, 1H, 1-H), 3.82–3.85 (m, 1H, 1-H), 5.08 (dd, *J*=15.3, 8.4 Hz, 1H, 5-H), 5.26–5.33 (m, 1H, 6-H), 7.31–7.41 (m, 9H, aryl), 7.66 (dd, *J*=7.6, 1.5 Hz, 4H, aryl), 7.77 (d, *J*=8.4 Hz, 2H, aryl); δ_C (100 MHz, $CDCl_3$) 16.0 (2-CH_3), 19.2 (*C*(CH_3)$_3$), 21.6 (4-CH_3), 21.8 (CH_3 aryl), 26.9 (C(*C*H_3)$_3$), 28.7 (C-7), 30.6 (C-2), 32.4 (C-8), 34.2 (C-4), 40.0 (C-3), 63.3 (C-9), 75.7 (C-1), 127.6 (CH aryl), 127.9 (CH aryl), 128.9 (C-6), 129.5 (CH aryl), 129.8 (CH aryl), 133.2 (C aryl), 134.0 (C aryl), 135.4 (C-5), 135.5 (CH aryl), 144.5 (*C*CH_3 aryl); HRMS (ESI): $[M+Na]^+$ calcd for $C_{34}H_{46}O_4SSiNa$ 601.27837, found 601.27831.

*4.1.17. (4E,6R,8R)-1-{[tert-Butyl(diphenyl)silyl]oxy}-6,8-dimethyl-4-decene (**42**).* To a solution of tosylate **41** (2.95 g, 5.09 mmol) and Cu(I)Br·SMe_2 complex (1.26 g, 6.11 mmol) in THF (45 mL) was added MeMgCl (18.7 mL, 56.1 mmol, 3 M in THF) −80 °C in a dropwise fashion. Stirring was continued for 1 h at −80 °C and 36 h at 0 °C. Then the mixture was treated with satd NH_4Cl solution and extracted with Et_2O (3×70 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave alkene **42** (2.06 g, 96%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 9:1) 0.83; $[\alpha]_D^{20}$ −9.9 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.80 (d, *J*=6.6 Hz, 3H, 8-CH_3), 0.81–0.85 (m, 3H, 10-H), 0.91 (d, *J*=6.6 Hz, 3H, 6-CH_3), 0.94–1.01 (m, 1H, 7-H), 1.05 (s, 9H, ^{t}Bu), 1.07–1.14 (m, 1H, 7-H), 1.17–1.36 (m, 3H, 8-H, 9-H), 1.58–1.65 (m, 2H, 2-H), 2.07 (q, *J*=6.9 Hz, 2H, 3-H), 2.11–2.17 (m, 1H, 6-H), 3.66 (t, *J*=6.4 Hz, 2H, 1-H), 5.16–5.22 (m, 1H, 5-H), 5.28–5.35 (m, 1H, 6-H), 7.35–7.42 (m, 6H, aryl), 7.67 (dd, *J*=7.8, 1.7 Hz, 4H, aryl); δ_C (100 MHz, $CDCl_3$) 11.3 (C-10), 19.0 (8-CH_3), 19.2 (*C*(CH_3)$_3$), 21.8 (6-CH_3), 28.8 (C-2), 30.0 (C-9), 31.8 (C-3), 32.6 (C-8), 34.4 (C-6), 44.4 (C-7), 63.3 (C-1), 127.6 (CH aryl), 127.8 (C-4), 129.5 (CH aryl), 134.2 (C aryl), 135.6 (CH aryl), 136.8 (C-5); HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{42}OSiNa$ 445.29026, found 445.29036.

*4.1.18. (4E,6R,8R)-6,8-Dimethyldec-4-en-1-ol (ent-**21**).* A solution of silyl ether **42** (1.78 g, 4.21 mmol) and TBAF (1.86 g, 5.9 mmol) was stirred for 4 h at room temperature. Then, satd NH_4Cl solution was added and the mixture extracted with Et_2O (3×40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave alkenol *ent*-**21** (706 mg, 91%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 4:1) 0.39; $[\alpha]_D^{20}$ −33.4 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.80 (d, *J*=6.4 Hz, 3H, 8-CH_3), 0.81–0.85 (m, 3H, 10-H), 0.92 (d, *J*=6.6 Hz, 3H, 6-CH_3),

0.94–1.01 (m, 1H, 7-H), 1.05–1.14 (m, 1H, 7-H), 1.18–1.35 (m, 3H, 8-H, 9-H), 1.42 (br, 1H, OH), 1.58–1.65 (m, 2H, 2-H), 2.06 (q, J=6.9 Hz, 2H, 3-H), 2.16 (ddd, J=14.4, 7.0 Hz, 1H, 6-H), 3.63 (t, J=6.6 Hz, 2H, 1-H), 5.20–5.26 (m, 1H, 5-H), 5.32–5.39 (m, 1H, 4-H); δ_C (100 MHz, $CDCl_3$) 11.3 (C-10), 18.8 (8-CH_3), 21.8 (6-CH_3), 28.9 (C-3), 30.0 (C-9), 31.9 (C-2), 32.5 (C-8), 34.4 (C-6), 44.4 (C-7), 62.6 (C-1), 127.5 (C-4), 137.2 (C-5); HRMS (ESI): $[M+Na]^+$ calcd for $C_{12}H_{24}ONa$ 207.17248, found 207.17221.

*4.1.19. (4E,6R,8R)-6,8-Dimethyldec-4-enal (ent-**22**).* A mixture of alcohol **21** (990 mg, 5.37 mmol), Dess–Martin periodinane (DMP, 3.99 g, 9.4 mmol), and $NaHCO_3$ (2.1 g, 24.17 mmol) in CH_2Cl_2 (20 mL) was stirred for 2 h at room temperature. Then water (30 mL) was added, and the mixture extracted with CH_2Cl_2 (3×70 mL). The combined organic layers were washed with a mixture of satd $NaHCO_3$/$Na_2S_2O_3$ solutions (50 mL, 1:1), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 4:1) gave aldehyde *ent*-**22** (860 mg, 88%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 4:1) 0.7; $[\alpha]_D^{20}$ −32.6 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.80 (d, J=6.4 Hz, 3H, 8-CH_3), 0.83 (t, J=7.3 Hz, 3H, 10-H), 0.92 (d, J=6.6 Hz, 3H, 6-CH_3), 0.94–1.01 (m, 1H, 7-H), 1.05–1.14 (m, 1H, 7-H), 1.18–1.34 (m, 3H, 8-H, 9-H), 2.10–2.20 (m, 1H, 6-H), 2.32 (q, J=7.2 Hz, 2H, 3-H), 2.45–2.49 (m, 2H, 2-H), 5.23–5.28 (m, 1H, 5-H), 5.35 (dt, J=15.3, 6.2 Hz, 1H, 4-H); δ_C (100 MHz, $CDCl_3$) 11.3 (C-10), 18.9 (8-CH_3), 21.6 (6-CH_3), 25.2 (C-3), 29.9 (C-9), 31.9 (C-8), 34.3 (C-6), 43.6 (C-2), 44.2 (C-7), 125.8 (C-4), 138.0 (C-4), 202.5 (C-1).

*4.1.20. (4S)-3-{(2S,3R,6E,8R,10R)-2-[4-(Allyloxy)benzyl]-3-hydroxy-8,10-dimethyldodec-6-enoyl}-4-benzyl-1,3-oxazolidin-2-one (**43**).* To a cooled solution of aldol reagent **32** (100 mg, 0.274 mmol) in CH_2Cl_2 (4.0 mL) was added slowly $TiCl_4$ (32 μL, 0.288 mmol) at 0 °C followed by the immediate addition of (−)-spartein (160 μL, 0.684 mmol). The mixture was stirred for 1.5 h at 0 °C. It was cooled to −80 °C and then a solution of aldehyde *ent*-**22** (54 mg, 0.301 mmol), dissolved in CH_2Cl_2 (1.0 mL) was added dropwise. The mixture was allowed to warm to 0 °C within 1 h. Now satd NH_4Cl solution (2 mL) was added and the mixture extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 2:1) gave aldol product **43** (105 mg, 70%) as a slightly yellow oil. R_f (petroleum ether/ethyl acetate, 3:1) 0.23; $[\alpha]_D^{20}$ +3.3 (*c* 0.25, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.81 (d, J=6.4 Hz, 3H, 10′-CH_3), 0.81–0.85 (m, 3H, 12′-H), 0.93 (d, J=6.6 Hz, 3H, 8′-CH_3), 0.96–1.01 (m, 1H, 9′-H), 1.07–1.14 (m, 1H, 9′-H), 1.18–1.35 (m, 3H, 10′-H, 11′-H), 1.50–1.66 (m, 2H, 4′-H), 2.02–2.24 (m, 3H, 5′-H, 8′-H), 2.88 (dd, J=13.5, 3.1 Hz, 1H, CH_2 aryl), 2.96 (dd, J=13.6, 5.0 Hz, 1H, CH_2 aryl), 3.04–3.10 (m, 1H, CH_2 aryl), 3.92–4.00 (m, 2H, 3′-H, 4-H), 4.08 (t, J=8.4 Hz, 1H, 4-H), 4.45 (dd, J=5.3, 4.1 Hz, 2H, CH_2CH=CH_2), 4.50–4.55 (m, 1H, 2′-H), 4.59–4.64 (m, 1H, 5-H), 5.21 (dd, J=10.4, 1.3 Hz, 1H, 7′-H), 5.25–5.29 (m, 1H, CH_2CH=CH_2), 5.32–5.37 (m, 2H, 6′-H, CH_2CH=CH_2), 5.94–6.05 (m, 1H, CH_2CH=CH_2), 6.81 (d, J=8.7 Hz, 2H, aryl), 6.94–6.96 (m, 2H, aryl), 7.18 (d, J=8.4 Hz, 2H, aryl), 7.23–7.25 (m, 3H, aryl); δ_C (100 MHz, $CDCl_3$) 11.3 (C-12′), 19.0 (10′-CH_3), 21.8 (8′-CH_3), 29.1 (C-5′), 29.9 (C-11′), 31.8 (C-10′), 32.3 (C-4′), 33.7 (CH_2 aryl), 34.3 (CH_2 aryl), 37.3 (C-8′), 44.4 (C-9′), 49.3 (C-2′), 55.0 (C-5), 65.6 (C-4), 68.8 (CH_2CH=CH_2), 71.9 (C-3′), 114.7 (CH aryl), 117.6 (CH_2CH=CH_2), 127.2 (CH aryl), 127.3 (C-6′), 128.9 (CH aryl), 129.3 (CH aryl), 130.4 (CH aryl), 130.8 (C aryl), 133.3 (CH_2CH=CH_2), 135.1 (C aryl), 137.4 (C-7′), 153.3 (C-2), 157.3 (CO aryl), 175.2 (C-1′); HRMS (ESI): $[M+Na]^+$ calcd for $C_{34}H_{45}NO_5Na$ 570.31899, found 570.31908.

*4.1.21. (4S)-3-[(2S,3R,6E,8R,10R)-2-[4-(Allyloxy)benzyl]-3-(methoxymethoxy)-8,10-dimethyldodec-6-enoyl]-4-benzyl-1,3-oxazolidin-2-one (**44**).* To a solution of aldol adduct **43** (100 mg, 0.18 mmol) in CH_2Cl_2 (4 mL) were added $^iPr_2NEt$ (220 μL, 1.28 mmol), and MOMCl (160 μL, 2.0 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h. Then, satd $NaHCO_3$ solution was added and the mixture extracted with CH_2Cl_2 (3×40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 3:1) gave MOM ether **44** (97 mg, 90%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 3:1) 0.49; $[\alpha]_D^{20}$ +59.1 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.81 (d, J=6.4 Hz, 3H, 10′-CH_3), 0.82–0.85 (m, 3H, 12′-H), 0.93 (d, J=6.6 Hz, 3H, 8′-CH_3), 0.96–1.02 (m, 1H, 9′-H), 1.06–1.14 (m, 1H, 9′-H), 1.18–1.38 (m, 3H, 10′-H, 11′-H), 1.66–1.79 (m, 2H, 4′-H), 1.98–2.08 (m, 1H, 5′-H), 2.12–2.24 (m, 2H, 5′-H, 8′-H), 2.39 (dd, J=13.5, 9.2 Hz, 1H, $PhCH_2$), 2.86–2.93 (m, 2H, $PhCH_2$, CH_2 aryl), 3.04–3.10 (m, 1H, CH_2 aryl), 3.37 (s, 3H, OCH_3), 3.81–3.85 (m, 1H, 3′-H), 4.01 (dd, J=9.2, 2.3 Hz, 1H, 5-H), 4.08 (t, J=8.3 Hz, 1H, 2′-H), 4.45–4.47 (m, 2H, CH_2CH=CH_2), 4.56 (d, J=7.4 Hz, 1H, OCH_2OCH$_3$), 4.55–4.61 (m, 2H, 4-H), 4.70 (d, J=7.1 Hz, 1H, OCH_2OCH$_3$), 5.20–5.27 (m, 2H, 7′-H, CH_2CH=CH_2), 5.32–5.37 (m, 2H, 6′-H, CH_2CH=CH_2), 5.95–6.05 (m, 1H, CH_2CH=CH_2) 6.82 (d, J=8.7 Hz, 2H, aryl), 6.94 (dd, J=6.6, 2.5 Hz, 2H, aryl), 7.17–7.24 (m, 5H, aryl); δ_C (100 MHz, $CDCl_3$) 11.3 (C-12′), 19.0 (10′-CH_3), 21.8 (8′-CH_3), 28.9 (C-5′), 29.9 (C-11′), 31.8 (C-10′), 32.6 (C-4′), 33.2 (CH_2 aryl), 34.3 (CH_2 aryl), 37.3 (C-8′), 44.4 (C-5′), 48.1 (C-2′), 55.4 (OCH_3), 56.2 (C-4), 65.6 (C-5), 68.8 (CH_2CH=CH_2), 78.4 (C-3′), 96.4 (OCH_2OCH_3), 114.7 (CH aryl), 117.5 (CH_2CH=CH_2), 127.2 (CH aryl), 127.4 (C-6′), 128.8 (CH aryl), 129.4 (CH aryl), 130.2 (CH aryl), 131.2 (C aryl), 133.4 (CH_2CH=CH_2), 135.2 (C aryl), 137.2 (C-7′), 153.0 (C-2), 157.2 (CO aryl), 173.5 (C-1′); HRMS (ESI): $[M+Na]^+$ calcd for $C_{36}H_{49}NO_6H$ 592.36326, found 592.36352.

*4.1.22. (2S,3R,6E,8R,10R)-2-[4-(Allyloxy)benzyl]-3-(methoxymethoxy)-8,10-dimethyldodec-6-enoic acid (**45**).* To a solution of amide derivative **44** (215 mg, 0.36 mmol) in THF/H_2O (6 mL, 10:1) were added LiOH (61 mg, 1.45 mmol) and H_2O_2 (230 μL, 2.0 mmol, 30% in H_2O) at 0 °C followed by stirring of the mixture for 2 h at room temperature. Thereafter, $Na_2S_2O_3$ solution (10% in water) was added, the mixture acidified with 1 N HCl and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 3:2) gave acid **45** (130 mg, 85%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 2:1) 0.46; $[\alpha]_D^{20}$ −3.0 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.81 (d, J=6.4 Hz, 3H, 10-CH_3), 0.82–0.85 (m, 3H, 12-H), 0.91 (d, J=6.6 Hz, 3H, 8-CH_3), 0.94–1.01 (m, 1H, 9-H), 1.05–1.14 (m, 1H, 9-H), 1.17–1.36 (m, 3H, 10-H, 11-H), 1.64–1.69 (m, 2H, 4-H), 1.96–2.07 (m, 1H, 5-H), 2.10–2.20 (m, 2H, 5-H, 8-H), 2.71–2.77 (m, 1H, CH_2 aryl), 2.93–3.00 (m, 2H, CH_2 aryl, 2-H), 3.38 (s, 3H, OCH_2OCH_3), 3.76–3.80 (m, 1H, 3-H), 4.48–4.50 (m, 2H, CH_2CH=CH_2), 4.66 (dd, J=18.6, 6.9 Hz, 2H, OCH_2OCH_3), 5.19–5.34 (m, 3H, 6-H, 7-H, CH_2CH=CH_2), 5.37–5.41 (m, 1H, CH_2CH=C_{H2}), 5.99–6.09 (m, 1H, CH_2CH=CH_2), 6.82 (d, J=8.7 Hz, 2H, 3′-H, 5′-H), 7.09 (d, J=8.7 Hz, 2H, 2′-H, 6′-H); δ_C (100 MHz, $CDCl_3$) 11.3 (C-12), 19.0 (10-CH_3), 21.7 (8-CH_3), 28.5 (C-5), 29.9 (C-11), 31.6 (C-10), 31.8 (C-4), 32.6 (C-1), 34.3 (C-8), 44.3 (C-9), 51.3 (C-2), 56.0 (OCH_3), 68.8 (CH_2CH=CH_2), 78.2 (C-3), 96.6 (OCH_2OCH_3), 114.8 (CH aryl), 117.6 (CH_2CH=CH_2), 127.1 (C-6), 129.7 (CH aryl), 131.3 (C aryl), 133.4 (CH_2CH=CH_2), 137.5 (C-7), 157.2 (CO aryl), 177.6 (CO_2); HRMS (ESI): $[M+Na]^+$ calcd for $C_{26}H_{40}O_5Na$ 455.27680, found 455.27682.

*4.1.23. tert-Butyl (1S,2R,5E,7R,9R)-1-[4-(allyloxy)benzyl]-2-(methoxymethoxy)-7,9-dimethylundec-5-enylcarbamate (**46**).* A solution of acid **45** (57 mg, 0.13 mmol), Et_3N (56 μL, 0.37 mmol), and diphenylphosphoryl azide (DPPA, 73 μL, 0.26 mmol) in benzene (3 mL) was refluxed for 2 h. After cooling to room temperature, ^{t}BuOH (100 μL, 1.06 mmol) and KO^{t}Bu (120 mg, 1.06 mmol) were added

followed by refluxing of the mixture for 1.5 h. The mixture was treated with water and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-Boc-amine **46** (41 mg, 63%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 4:1) 0.54; $[\alpha]_D^{20}$ −36.5 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.80 (d, *J*=6.4 Hz, 3H, 10-CH_3), 0.81–0.85 (m, 3H, 12-H), 0.91 (d, *J*=6.6 Hz, 3H, 8-CH_3), 0.94–1.02 (m, 1H, 9-H), 1.05–1.13 (m, 1H, 9-H), 1.17–1.27 (m, 3H, 10-H, 11-H), 1.31 (s, 9H, ^{t}Bu), 1.48–1.57 (m, 1H, 4-H), 1.60–1.69 (m, 1H, 4-H), 1.97–2.09 (m, 1H, 5-H), 2.10–2.18 (m, 2H, 5-H, 8-H), 2.56–2.62 (m, 1H, 1-H), 2.83 (dd, *J*=14.2, 4.8 Hz, 1H, 1-H), 3.41 (s, 3H, OCH_3), 3.59 (br, 1H, 3-H), 3.93 (d, *J*=5.1 Hz, 1H, 2-H), 4.49 (d, *J*=5.3 Hz, 2H, CH_2CH=CH_2), 4.66 (dd, *J*=24.2, 6.9 Hz, 2H, OCH_2OCH$_3$), 4.97 (d, *J*=8.7 Hz, 1H, NH), 5.18–5.34 (m, 3H, 6-H, 7-H, CH_2CH=CH_2), 5.38 (dd, *J*=17.3, 1.5 Hz, 1H, CH_2CH=CH_2), 5.98–6.00 (m, 1H, CH_2C*H*=CH_2), 6.82 (d, *J*=8.7 Hz, 2H, 3′-H, 5′-H), 7.10 (d, *J*=8.7 Hz, 2H, 2′-H, 6′-H); δ_C (100 MHz, $CDCl_3$) 11.3 (C-12), 18.9 (10-CH_3), 21.7 (8-CH_3), 28.3 (C(*C*H$_3$)$_3$), 28.7 (C-11), 29.9 (C-5), 31.8 (C-10), 31.9 (C-4), 34.3 (C-1), 34.9 (C-8), 44.4 (C-9), 54.0 (OCH_3), 55.8 (C-7), 68.8 (C-7′), 78.9 (*C*(CH$_3$)$_3$), 81.4 (C-3), 97.3 (O*C*H$_2$OCH$_3$), 114.6 (C-3′, C-5′), 117.5 (C-9′), 127.2 (C-6), 129.6 (C-1′), 130.1 (C-2′, C-6′), 133.5 (C-8′), 137.4 (C-7), 155.4 (CO_2), 157.1 (C-4′); HRMS (ESI): $[M+H]^+$ calcd for $C_{30}H_{49}NO_5H$ 504.36835, found 504.36841.

*4.1.24. tert-Butyl (1S,2R,5E,7R,9R)-1-[4-(allyloxy)benzyl]-2-(methoxymethoxy)-7,9-dimethylundec-5-enyl(methyl)carbamate (**47**).* To a solution of *N*-Boc-amine **46** (39 mg, 0.08 mmol) in DMF (2 mL) was added NaH (4 mg, 0.16 mmol) at 0 °C. After stirring for 20 min at this temperature, methyl iodide (12 μL, 0.19 mmol) was added and the mixture allowed to reach room temperature. Stirring was continued for 10 h before water was added and the mixture was extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (petroleum ether/ethyl acetate, 9:1) gave *N*-methylamine **47** (38 mg, 95%) as a colorless oil. R_f (petroleum ether/ethyl acetate, 7:1) 0.21; $[\alpha]_D^{20}$ −40.0 (*c* 1.0, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.79 (d, *J*=6.4 Hz, 3H, 10-CH_3), 0.79–0.84 (m, 3H, 12-H), 0.91 (d, *J*=6.6 Hz, 3H, 8-CH_3), 0.94–1.02 (m, 1H, 9-H), 1.05–1.12 (m, 1H, 9-H), 1.15–1.39 (m, 3H, 10-H, 11-H), 1.30 (s, 9H, ^{t}Bu), 1.44–1.53 (m, 1H, 4-H), 1.60–1.70 (m, 1H, 4-H), 2.06–2.18 (m, 3H, 5-H, 8-H), 2.54 (s, 3H, NCH_3), 2.68 (br, 2H, 1-H), 3.04–3.10 (m, 1H, 3-H), 3.42 (s, 3H, OCH_2OCH_3), 3.61–3.80 (m, 1H, 2-H), 4.48 (d, *J*=5.3 Hz, 2H, CH_2CH=CH_2), 4.65–4.68 (m, 1H, OCH_2OCH$_3$), 4.71–4.75 (m, 1H, OCH_2OCH$_3$), 5.17–5.33 (m, 3H, 6-H, 7-H, CH_2CH=CH_2), 5.37 (dd, *J*=17.3, 1.5 Hz, 1H, CH_2CH=CH_2), 5.97–6.07 (m, 1H, CH_2C*H*=CH_2), 6.79–6.81 (m, 2H, 3′-H, 5′-H), 7.04 (d, *J*=8.7 Hz, 2H, 2′-H, 6′-H); δ_C (100 MHz, $CDCl_3$) 11.3 (C-12), 18.9 (10-CH_3), 21.7 (8-CH_3), 27.5 (C(*C*H$_3$)$_3$), 28.1 (C-11), 28.3 (NCH_3), 29.9 (C-5), 31.2 (C-10), 31.8 (C-4), 33.2 (C-1), 34.3 (C-8), 44.4 (C-9), 56.0 (C-2), 56.1 (OCH_2OCH_3), 68.9 (*C*H_2CH=CH_2), 79.1 (*C*(CH$_3$)$_3$), 79.5 (C-3), 96.5 (O*C*H$_2$OCH$_3$), 114.5, 114.6 (C-3′, C-5′), 117.5 (CH_2CH=CH_2), 127.7 (CH_2*C*H=CH_2), 127.9 (C-1′), 129.8, 129.9 (C-2′, C-6′), 133.4 (C-8′), 136.9 (C-7), 155.6 (CO_2), 157.1 (C-4′); HRMS (ESI): $[M+Na]^+$ calcd for $C_{31}H_{51}NO_5Na$ 540.36594, found 540.36508.

*4.1.25. tert-Butyl (1S,2R,5E,7R,9R)-1-(4-hydroxybenzyl)-2-(methoxymethoxy)-7,9-dimethylundec-5-enyl(methyl)carbamate (**48**).* To a solution of allyl ether **47** (38 mg, 0.073 mmol) in degassed THF (2 mL) were added $Pd(PPh_3)_4$ (8.5 mg, 0.01 mmol) and morpholine (65 μL, 0.8 mmol) followed by stirring of the mixture for 12 h at room temperature. The solvent was removed in vacuo and the residue purified by flash chromatography (petroleum ether/ethyl acetate, 3:1). The phenol **48** (28 mg, 79%) was obtained as a colorless oil. R_f (petroleum ether/ethyl acetate, 3:1) 0.25; $[\alpha]_D^{20}$ −54.7 (*c* 0.5, CH_2Cl_2); δ_H (400 MHz, $CDCl_3$) 0.79 (d, *J*=6.4 Hz, 3H, 10-CH_3), 0.80–0.84 (m, 3H, 12-H), 0.91 (d, *J*=6.6 Hz, 3H, 8-CH_3), 0.95–1.00 (m, 1H, 9-H), 1.04–1.28 (m, 4H, 9-H, 10-H, 11-H), 1.32 (s, 9H, ^{t}Bu), 1.44–1.55 (m, 1H, 4-H), 1.60–1.72 (m, 1H, 4-H), 2.03–2.17 (m, 3H, 5-H, 8-H), 2.58 (s, 3H, NCH_3), 2.74 (br, 2H, 1-H), 3.06 (dd, *J*=13.7, 2.3 Hz, 3-H), 3.44 (s, 3H, OCH_3), 3.61–3.76 (m, 1H, 2-H), 4.67 (d, *J*=6.9 Hz, 1H, OCH_2OCH$_3$), 4.75 (d, *J*=6.9 Hz, 1H, OCH_2OCH$_3$), 5.18–5.23 (m, 1H, 7-H), 5.28–5.35 (m, 1H, 6-H), 6.73 (d, *J*=8.4 Hz, 2H, 3′-H, 5′-H), 7.00 (d, *J*=8.4 Hz, 2H, 2′-H, 6′-H); δ_C (100 MHz, $CDCl_3$) 11.3 (C-12), 18.9 (10-CH_3), 21.8 (8-CH_3), 27.5 (C(*C*H$_3$)$_3$), 28.1 (C-11), 28.3 (NCH_3), 29.9 (C-5), 31.2 (C-10), 31.8 (C-4), 33.2 (C-1), 34.3 (C-8), 44.4 (C-9), 55.0 (OCH_2OCH_3), 55.1 (C-2), 79.1 (*C*(CH$_3$)$_3$), 80.0 (C-3), 96.5 (O*C*H$_2$OCH$_3$), 115.1, 115.2 (C-3′, C-5′), 127.7 (C-6), 127.9 (C-1′), 129.8, 130.0 (C-2′, C-6′), 137.0 (C-7), 154.8 (CO_2), 155.9 (C-4′); HRMS (ESI): $[M+Na]^+$ calcd for $C_{28}H_{47}NO_5Na$ 500.33464, found 500.33460.

*4.1.26. 4-[(2S,3R,6E,8R,10R)-3-Hydroxy-8,10-dimethyl-2-(methylamino)dodec-6-enyl]phenol (tyroscherin **2**).* To a solution of carbamate **48** (10 mg, 0.021 mmol) in MeOH (2 mL) was added concd HCl (30 μL) followed by stirring of the mixture for 1 h at 50 °C. The solvent was evaporated in vacuo and the residue purified by flash chromatography ($CHCl_3$/MeOH, 5:1) yielding tyroscherin (**2**) (6.3 mg, 90%) as a slightly yellow oil.

Preparation of the TFA salt: A solution of tyroscherin amine (6 mg, 0.02 mmol) in CH_2Cl_2 (5 mL) was treated with TFA (50 μL) followed by stirring of the mixture for 1 h at room temperature. The solvent was removed in vacuo and the residue further dried on an oil pump. The salt was obtained in quantitative yield as a slightly yellow oil. R_f ($CHCl_3$/MeOH, 5:1) 0.31; $[\alpha]_D^{20}$ −19.0 (*c* 0.35, MeOH); δ_H (400 MHz, $CDCl_3$) 0.82 (d, *J*=6.1 Hz, 3H, 10-CH_3), 0.83–0.86 (m, 3H, 12-H), 0.90 (d, *J*=6.6 Hz, 3H, 8-CH_3), 0.98 (ddd, *J*=13.2, 8.4, 5.3 Hz, 1H, 9-H), 1.07–1.16 (m, 1H, 11-H), 1.19–1.23 (m, 1H, 9-H), 1.24–1.33 (m, 2H, 10-H, 11-H), 1.45–1.60 (m, 2H, 4-H), 1.99 (dd, *J*=14.2, 7.4 Hz, 1H, 5-H), 2.10–2.25 (m, 2H, 5-H, 8-H), 2.62 (s, 3H, NCH_3), 2.83–2.94 (m, 1H, 1-H), 3.31–3.38 (m, 1H, 2-H), 3.83 (d, *J*=8.1 Hz, 1H, 3-H), 5.18–5.24 (m, 1H, 7-H), 5.30–5.37 (m, 1H, 6-H), 6.77 (d, *J*=7.9 Hz, 2H, 3′-H, 5′-H), 7.11 (d, *J*=7.9 Hz, 2H, 2′-H, 6′-H); δ_C (100 MHz, $CDCl_3$) 11.7 (C-12), 19.3 (10-CH_3), 22.3 (8-CH_3), 29.9 (C-5), 31.1 (C-11), 32.4 (NCH_3, C-1), 33.0 (C-4), 33.1 (C-10), 35.7 (C-8), 45.5 (C-9), 66.8 (C-2), 68.7 (C-3), 116.8 (C-3′, C-5′), 127.6 (C-1′), 128.4 (C-6), 131.3 (C-2′, C-6′), 138.7 (C-7), 157.9 (C-4′); HRMS (ESI): $[M+H]^+$ calcd for $C_{21}H_{36}NO_2H$ 334.27406, found 334.27418.

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Supplementary data

Supplementary data associated with this article (remaining procedures for Scheme 1–3, copies of NMR spectra) can be found in the online version, at doi:10.1016/j.tet.2010.02.034.

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