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First Stereoselective Total Synthesis and Biological Evaluation of Amphidinin B and Its Analogues

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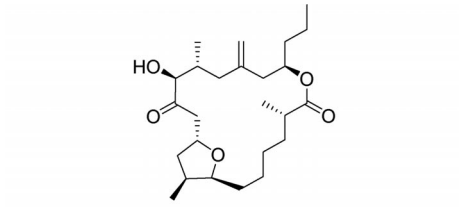
A highly stereoselective first total synthesis of amphidinin B is described. The key steps involved in this synthesis are the generation of the *exo*-double bond in the C^1–C^9 segment, the Barbier allylation, enzymatic kinetic resolution, and the construction of the C^{10}–C^{21} segment by Sharpless asymmetric epoxidation, base-induced epoxide ring-opening, radical cyclization, diastereoselective reduction of the *exo*-cyclic double bond, one-pot allylation followed by debenzylation, Evans alkylation, and Yamaguchi esterification.

Introduction

Marine dinoflagellates of the genus *Amphidinium* have been recognized as a source of novel secondary metabolites with interesting biological activity.[1] Despite their common origin and high toxicity against various cancer cell lines, the linear polyketides possess a high degree of structural diversity, incorporating many variegated molecular scaffolds.[2] Amphidinin B (**2**) was isolated from the extracts of the strain Y-56 of the dinoflagellate *Amphidinium* sp., which is a linear polyketide possessing a trisubstituted tetrahydrofuran moiety, an *exo*-methylene, three branched methyl groups and two carboxyl groups. The structure of **2** was established by extensive NMR spectroscopic studies and the absolute stereochemistry was established by modified Mosher's method.[3] The backbone of **2** was the same as the carbon framework of the 19-membered macrolide, amphidinolide T1 (**1**).[4] Biogenetically, amphidinin B (**2**) may be related to amphidinolide T1 (**1**) (Scheme 1).



Scheme 1. Structures of amphidinolide T1 (**1**) and amphidinin B (**2**).

Because of the low amounts available for biological evaluation and because of its unique molecular architecture, amphidinin B (**2**) has attracted significant attention from a number of synthetic chemists. In a continuation of our synthesis of complex natural products, such as amphidinolide T1 (**1**),[5] we herein report a novel, convergent and stereoselective approach to the total synthesis of amphidinin B (**2**).

Our retrosynthetic analysis of amphidinin B (**2**) is shown in Scheme 2. The formation of the amphidinin B was envisaged starting from terminal diol **3**, which could, in turn, be obtained by Yamaguchi esterification[6] between the trisubstituted tetrahydrofuran fragment **4** and the homoallyl ether fragment **5**. Synthons **4** and **5** could be obtained from **6** and **7**, respectively.

The synthesis of compound **4** began from the known mono-benzyl ether **6** (Scheme 3), which was oxidized to the corresponding aldehyde and further homologated by a two-carbon Wittig olefination to afford α,β-unsaturated ester **8** (*E* isomer) as the sole product (81% over two steps). Reduction of compound **8** with $LiAlH_4/AlCl_3$ afforded the allylic alcohol in 80% yield. Sharpless asymmetric epoxid-

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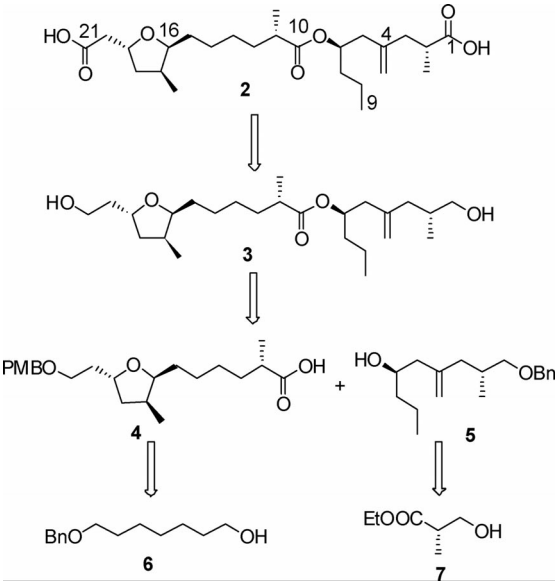
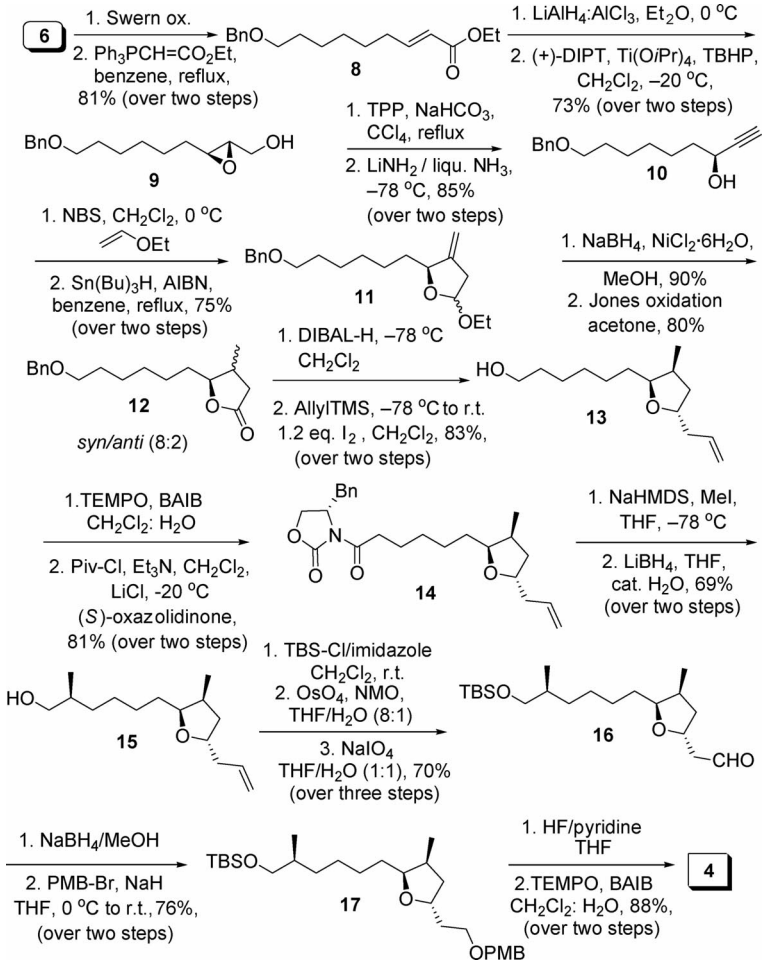


Scheme 2. Retrosynthetic analysis of amphidinin B.

ation of the allyl alcohol using (+)-diisopropyl tartrate [(+)-DIPT], $Ti(OiPr)_4$ and TBHP at –20 °C gave the epoxy alcohol **9** in 91% yield with 94% *ee*.[7] Treatment of compound **9** with triphenylphosphane (TPP) and carbon tetrachloride in the presence of $NaHCO_3$ under reflux conditions, followed by subsequent base-induced dehydrohalogenation using the methodology developed by us,[8] gave alkynol **10** in 88% overall yield. Compound **10** was then reacted with ethyl vinyl ether and *N*-bromosuccinimide (NBS) to afford the corresponding bromo acetal, which, upon radical cyclization[9] in the presence of nBu_3SnH and 2,2′-azobis(isobutyronitrile) (AIBN) in refluxing benzene, afforded homoallylic lactol ether **11** in 75% overall yield for the two steps. Diastereoselective reduction of compound **11** with $NaBH_4$ and $NiCl_2{\cdot}6H_2O$[10] in methanol followed by Jones oxidation[11] afforded a mixture of *syn* and *anti* isomers **12** in an 8:2 ratio (80% yield over two steps), which were separated by column chromatography.

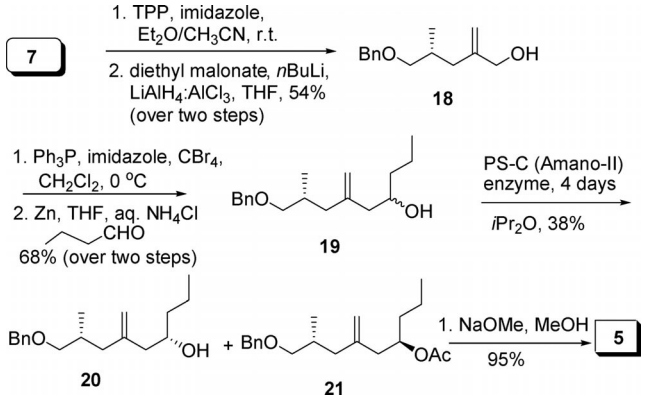
Reduction of the *syn*-lactone with diisobutylaluminum hydride (DIBAL-H) gave the lactol, which was subsequently treated with allyltrimethylsilane in the presence of a stiochiometric amount of iodine to accomplish allylation with a concomitant debenzylation,[12] resulting in the formation of the allylated product **13** in 83% yield as the only product. The primary hydroxyl group of **13** was converted into the carboxyl group by oxidation with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) and [bis(acetoxy)iodo]-benzene (BAIB) in a mixture of dichloromethane and water.[13] The resulting acid was coupled with chiral (*S*)-



Scheme 3. Synthesis of segment **4**.

oxazolidin-2-one using mixed anhydride conditions, to furnish **14** in 81% yield over two steps.[14] Diastereoselective alkylation of the sodium-enolate of **14** with iodomethane, followed by reductive cleavage of the chiral auxiliary, afforded alcohol **15** as the only isomer in 69% overall yield (Scheme 1). The resulting hydroxyl group was converted into its *tert*-butyldimethylsilyl (TBS) ether followed by dihydroxylation with a catalytic amount of OsO_4 and a stoichiometric amount of 4-methylmorpholine *N*-oxide (NMO). The oxidative cleavage of the diol using $NaIO_4$ gave aldehyde **16** in 70% yield over three steps.[15] The resulting aldehyde was reduced with $NaBH_4$ to afford the corresponding alcohol, which was subsequently protected as its *p*-methoxybenzyl (PMB) ether using *p*-methoxybenzyl bromide (PMBBr) and sodium hydride to afford **17** in 76% over two steps. Exposure of TBS ether **17** to HF/Py complex afforded the primary hydroxyl compound, which, on subsequent oxidation with TEMPO/BAIB,[13] gave acid **4** in 88% yield (two steps).

The synthesis of segment **5** (Scheme 4) began with monobenzyl ether **7**, which can be prepared from the commercially available methyl (*S*)-3-hydroxy-2-methylpropionate.[16] Iodination of **7** with TPP, imidazole and molecular iodine afforded the corresponding iodo compound in 90% yield, which was alkylated with diethyl malonate and then subjected to base-induced reductive elimination using *n*BuLi as base and AlH_3 (alane) as reducing agent to afford the substituted allyl alcohol **18** exclusively in 60% yield.[17] The conversion of substituted allyl alcohol **18** into the corresponding allyl bromide was achieved by using TPP/CBr_4. The resulting allyl bromide was treated with *n*-butanal under conditions developed by Barbier[18] to afford a racemic homoallyl alcohol **19** in 68% yield over two steps. Enzymatic kinetic resolution of **19** using lipase PS-C "Amano" II afforded (*R*)-homoallylic acetate **21** (38% yield with 98% *ee*).[19] The undesired isomer **20** was converted into the required isomer by oxidation, followed by reduction and a subsequent enzymatic resolution. Deacetylation of **21** with sodium methoxide gave the segment **5** in 95% yield.

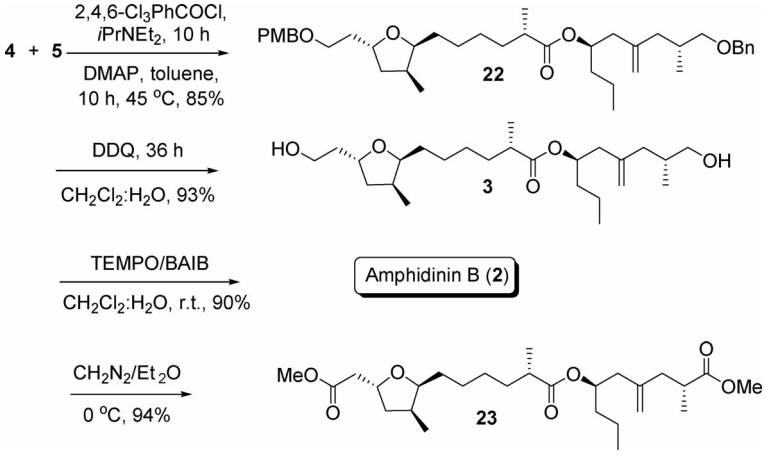


Scheme 4. Synthesis of the segment **5**.

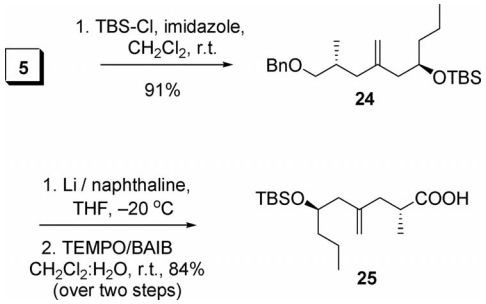
With the successful synthesis of the two fragments **4** and **5**, the next task was to assemble both of the segments using an intermolecular Yamaguchi esterification to obtain compound **22** in 85% yield (Scheme 5).[6] Oxidative removal of the terminal benzyl and *p*-methoxybenzyl groups in **22** using 30 equiv. of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a mixture of dichloromethane and water gave the terminal diol **3** in 93% yield.[20] Oxidation of the primary hydroxyl groups of **3** to the corresponding carboxyl groups was achieved using TEMPO/BAIB to afford amphidinin B (**2**) in 90% yield.[21] The spectral (^1H and ^{13}C NMR) and analytical data were in good agreement with the data reported in the literature for the natural product.[3] Amphidinin B (**2**) was converted into its corresponding methyl ester using diazomethane to afford **23** in 94% yield.

Synthesis of compound **25** began with segment **5**. Protection of the secondary hydroxyl group in segment **5** as its TBS ether gave **24** in 91% yield (Scheme 6). Treatment of compound **24** with lithium/naphthalene[22] afforded the primary hydroxyl compound, which, on subsequent oxidation with TEMPO/BAIB, gave compound **25** in 93% yield (two steps).

In a recent report, amphidinolide T1 (**1**) was shown to exhibit cytotoxicity (IC_{50}) effects on mammalian cells in the micromolar range. To further understand the effects of amphidinin B (**2**) and its synthetic intermediates, the efficacy



Scheme 5. Completion of total synthesis of amphidinin B (**2**).



Scheme 6. Synthesis of compound **25**.

of these compounds were tested against MCF-7, a breast cancer cell line. The 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay was performed by following the previously reported protocol in 96-well plates.[23] The IC_{50} values for the compounds are summarized in Table 1. Surprisingly, amphidinin B (**2**), with the terminal carboxylic acids, displayed about 100 times better activity than its cyclic analog. Esterified amphidinin B (**23**) or reduced amphidinin B (**3**) decreased the efficiency of amphidinin B (**2**) by ten-fold and still displayed better activity than amphidinolide T1 (**1**). To summarize, the acyclic compounds show much better efficiency in killing cancer cells than their cyclic analogs. Moreover, when the two fragments of amphidinin B (**2**) were tested separately, only one (fragment **25**), with the aliphatic chain, displayed efficiency as good as amphidinolide T1 (**1**); the second half (fragment **4**) is ineffective even at 1 mM concentration (Table 1).

Table 1. Biological activity of amphidinin B and its analogues.

Entry	Compound	IC_{50} [μM]
1	**1**	73.5
2	**2**	0.83
3	**4**	1000
4	**23**	9.9
5	**25**	99.7
6	**3**	7.9

Conclusions

A highly convergent and stereoselective first total synthesis of amphidinin B (**2**) has been achieved that confirmed the absolute configuration and provided sufficient quantities for biological evaluation. The stereocenters of the substituted tetrahydrofuran moiety were obtained by Sharpless asymmetric epoxidation, diastereoselective reduction of the exocyclic double bond, and allylation of the five-membered ring oxa-carbenium ion using our developed methodology.

Experimental Section

General Remarks: Air- and/or moisture-sensitive reactions were carried out in anhydrous solvents under an atmosphere of argon in oven- or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, benzene, toluene, and diethyl ether from Na and benzophenone; CH_2Cl_2 from CaH_2; MeOH, EtOH from Mg cake. Commercial reagents were used without purification. Column chromatography was carried out using silica gel (60–120 mesh) and (230–400 mesh). Specific optical rotations $[\alpha]_D$ are given in 10^{-1} deg·cm^2·g^{-1}. Infrared spectra were recorded either in $CHCl_3$ or neat (as mentioned) and are reported in wave numbers (cm^{-1}). ^{1}H and ^{13}C NMR chemical shifts are reported in ppm downfield from tetramethylsilane and coupling constants (*J*) are reported in Hertz. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, and br = broad.

7-(Benzyloxy)heptanal (6a): To a solution of oxalyl chloride (6.1 mL, 71.53 mmol) in CH_2Cl_2 (60 mL) at –78 °C was added dimethyl sulfoxide (10.8 mL, 152.56 mmol) over 20 min. The reaction mixture was stirred for an additional 15 min and then alcohol **6** (10.63 g, 47.66 mmol) dissolved in CH_2Cl_2 (30 mL) was added slowly by using a cannula. After 30 min, triethylamine (33.2 mL, 238.4 mmol) was added dropwise to the reaction mixture. The reaction was allowed to warm to r.t. over 1 h. After completion of the reaction (monitored by TLC), it was quenched with water (120 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine, dried with anhydrous Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (ethyl acetate/hexane, 1:9) to afford aldehyde **6a** (8.4 g, 90%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.76 (s, 1 H, CHO), 7.37–7.22 (m, 5 H, PhH), 4.49 (s, 2 H, OCH_2Ph), 3.45 (t, *J* = 6.0 Hz, 2 H, CH_2OBn), 2.43 (td, *J* = 7.5, 1.5 Hz, 2 H, CH_2CHO), 1.72–1.57 (m, 4 H, $(CH_2)_2$), 1.49–1.31 (m, 4 H, $(CH_2)_2$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 202.6, 138.7, 128.2, 127.5, 127.4, 72.8, 70.2, 43.8, 29.5, 28.9, 25.9, 22.0 ppm. IR (neat): $\tilde{\nu}$ = 2933, 2857, 1723, 1099, 737, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{21}O_2$ $[M + H]^+$ 221.1541; found 221.1534.

Ethyl (*E*)-9-(Benzyloxy)-2-nonenoate (8): To a stirred solution of aldehyde **6a** (8.08 g, 36.74 mmol) in benzene (100 mL), was added $Ph_3P{=}CHCO_2Et$ (19.18 g, 55.11 mmol) in one portion. The reaction was heated to reflux for 4 h at 80 °C. Upon completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (ethyl acetate/hexane, 0.5:9.5) afforded α,β-unsaturated ester **8** (9.82 g, 90%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H, PhH), 7.00–6.82 (m, 1 H, $CH{=}CHCO_2Et$), 5.77 (d, *J* = 15.5 Hz, 1 H, $CH{=}CHCO_2Et$), 4.47 (s, 2 H, OCH_2Ph), 4.16 (q, *J* = 6.9 Hz, 2 H, OCH_2CH_3), 3.42 (t, *J* = 6.9 Hz, 2 H, CH_2OBn), 2.27–2.13 (m, 2 H, $CH_2CH{=}CHCO_2Et$), 1.66–1.34 (m, 8 H, $(CH_2)_4$), 1.30 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 185.8, 168.3, 157.8, 147.5, 146.7, 146.6, 140.5, 92.0, 89.5, 79.2, 51.2, 48.8, 48.1, 47.1, 45.1, 33.4 ppm. IR (neat): $\tilde{\nu}$ = 2932, 2856, 1719, 1653, 1267, 1183, 1101, 737, 699 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{26}O_3Na$ $[M + Na]^+$ 313.1779; found 313.1771.

(*E*)-9-(Benzyloxy)-2-nonen-1-ol (8a): To a stirred suspension of $LiAlH_4$ (1.67 g, 44.27 mmol) in anhydrous Et_2O (60 mL) at 0 °C under an N_2 atmosphere, was added slowly a solution of $AlCl_3$ (1.97 g, 14.75 mmol) in Et_2O (20 mL). The reaction mixture was stirred at the same temperature for 30 min. To this stirred suspension, was added dropwise a solution of ester **8** (8.57 g, 29.52 mmol) in anhydrous Et_2O (20 mL) over a period of 10 min and stirred at 0 °C for an additional 1 h. Upon completion of the reaction (monitored by TLC), the reaction mixture was quenched with ice pieces and filtered through Celite and the residue was washed with hot ethyl acetate. The combined organic layer was dried with anhydrous Na_2SO_4, concentrated and purification by column chromatography (ethyl acetate/hexane, 2:8) to give the allyl alcohol

8a (5.86 g, 80%) as a viscous liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 5 H, PhH), 5.65–5.57 (m, 2 H, CH=CH), 4.47 (s, 2 H, OCH_2Ph), 4.02 (d, J = 3.9 Hz, 2 H, CH=CHCH_2OH), 3.43 (t, J = 7.0 Hz, 2 H, CH_2OBn), 2.09–1.96 (m, 2 H, CH_2CH=CHCH$_2$OH), 1.69–1.51 (m, 3 H, CH_2CH), 1.46–1.24 (m, 5 H, $(CH_2)_2CH$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.7, 133.0, 129.0, 128.3, 127.6, 127.5, 72.9, 70.4, 63.6, 32.2, 29.6, 29.1, 29.0, 26.0 ppm. IR (neat): $\tilde{\nu}$ = 3426, 2927, 2854, 1456, 1095, 736, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{24}O_2Na$ [M + Na]$^+$ 271.1673; found 271.1666.

(2*S*,3*S*)-3-[6-(Benzyloxy)hexyl]oxiran-2-ylmethanol (9): Anhydrous CH_2Cl_2 (50 mL) was added to activated molecular sieves powder (4 Å, 2.3 g) and the suspension was cooled to –20 °C under an N_2 atmosphere. L-(+)-DIPT (0.9 mL, 4.2 mmol) and Ti(O*i*Pr)$_4$ (1.3 mL, 4.2 mmol) were added with stirring and the resulting mixture was stirred for 30 min at –20 °C. The allyl alcohol **8a** (5.2 g, 21.0 mmol) in anhydrous CH_2Cl_2 (6 mL) was added and the resulting mixture was stirred for another 30 min at –20 °C. *t*Butyl hydroperoxide (TBHP; 5.8 M in toluene, 14.4 mL, 41.9 mmol) was then added and the resulting mixture was stirred at the same temperature for 8 h, then warmed to 0 °C. Upon completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (25 mL) and stirred at r.t. for 2 h. Aqueous NaOH (30%), saturated with NaCl (8 mL) was then added and the resulting mixture was stirred vigorously at r.t. for a further 30 min. The resulting mixture was filtered through a Celite pad and the filter cake washed well with CH_2Cl_2. The organic phase was separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. Removal of the solvent under reduced pressure and purification by flash column chromatography (ethyl acetate/hexane, 3:7) afforded **9** (5.03 g, 91%) as a colorless viscous liquid. $[\alpha]_D^{25}$ = –19.4 (c = 1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.17 (m, 5 H, PhH), 4.46 (s, 2 H, OCH_2Ph), 3.83 (d, J = 13.3 Hz, 1 H, epoxy-CH_2OH), 3.54 (d, J = 12.5 Hz, 1 H, epoxy-CH_2OH), 3.43 (t, J = 6.2 Hz, 2 H, CH_2OBn), 2.93–2.81 (m, 2 H, epoxy-H), 2.11 (br., 1 H, OH), 1.65–1.24 (m, 10 H, $(CH_2)_5$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.3, 128.0, 127.3, 127.2, 72.6, 70.0, 61.6, 58.4, 55.8, 31.2, 29.3, 28.9, 25.8, 25.6 ppm. IR (neat): $\tilde{\nu}$ = 3430, 2930, 2856, 1456, 1100, 737, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{24}O_3Na$ [M + Na]$^+$ 287.1623; found 287.1622.

(2*S*,3*R*)-2-[6-(Benzyloxy)hexyl]-3-(chloromethyl)oxirane (9a): To a stirred solution of triphenylphosphane (5.96 g, 22.8 mmol) in anhydrous CCl_4 (50 mL), was added a solution of epoxy alcohol **9** (5.0 g, 18.9 mmol) in CCl_4 (10 mL) followed by $NaHCO_3$ (10 mol-%). The reaction mixture was stirred at reflux temperature for 24 h. After completion of the reaction (monitored by TLC), the mixture was cooled to 30 °C and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane, 1:9) to afford epoxy chloride **9a** (4.77 g, 90%) as a colorless viscous liquid. $[\alpha]_D^{25}$ = –9.8 (c = 1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 5 H, PhH), 4.45 (s, 2 H, OCH_2Ph), 3.64–3.53 (m, 1 H, epoxy-CH_2Cl), 3.46–3.31 (m, 3 H, epoxy-CH_2Cl and CH_2OBn), 2.91 (td, J = 5.5, 2.1 Hz, 1 H, epoxy-H), 2.78 (td, J = 5.5, 2.1 Hz, 1 H, epoxy-H), 1.66–1.26 (m, 10 H, $(CH_2)_5$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.6, 128.3, 127.5, 127.4, 72.8, 70.3, 59.0, 57.0, 44.7, 31.3, 29.6, 29.0, 26.0, 25.7 ppm. IR (neat): $\tilde{\nu}$ = 2929, 2855, 1455, 1101, 736, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{23}O_2NaCl$ [M + Na]$^+$ 305.1284; found 305.1272.

(3*S*)-9-(Benzyloxy)-1-nonyn-3-ol (10): A catalytic amount of ferric nitrate was added to liquid ammonia (70 mL) at –78 °C, followed by the slow addition of freshly cut fine lithium metal pieces (0.64 g, 92.0 mmol), and the mixture was stirred for 30 min. A solution of epoxy chloride **9a** (4.28 g, 15.34 mmol) in THF (2.5 mL) was added dropwise at –78 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched by addition of some solid ammonium chloride and the ammonia was allowed to evaporate. The residue was dissolved in diethyl ether and filtered. The filtrate was dried with Na_2SO_4 and the crude product was purified by column chromatography (ethyl acetate/hexane, 2:8) to afford alkynol **10** (3.59 g, 95%) as a liquid. $[\alpha]_D^{25}$ = –1.4 (c = 1.8, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.17 (m, 5 H, PhH), 4.47 (s, 2 H, OCH_2Ph), 4.29 (t, J = 5.5 Hz, 1 H, C*H*OH-alkyne), 3.43 (t, J = 6.2 Hz, 2 H, CH_2OBn), 2.37 (d, J = 2.3 Hz, 1 H, alkyne-H), 1.95–1.21 (m, 10 H, $(CH_2)_5$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.0, 127.4, 127.3, 85.1, 72.5, 72.3, 70.0, 61.6, 37.3, 29.3, 28.8, 25.8, 24.7 ppm. IR (neat): $\tilde{\nu}$ = 3409, 2931, 2857, 1455, 1097, 742, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{22}O_2Na$ [M + Na]$^+$ 269.1517; found 269.1514.

(3*S*)-9-(Benzyloxy)-3-(2-bromo-1-ethoxyethoxy)-1-nonyne (10a): To a stirred solution of alkynol **10** (3.58 g, 14.57 mmol) and NBS (3.11 g, 17.48 mmol) in anhydrous CH_2Cl_2 (50 mL) under an N_2 atmosphere at 0 °C, was added ethyl vinyl ether (3.3 mL, 34.96 mmol). The reaction mixture was then brought to r.t. and stirred for 1 h. Upon completion of the reaction (monitored by TLC), solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/hexane, 0.5:9.5) as quickly as possible to obtain the bromo acetal **10a** (4.77 g, 83%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 5 H, PhH), 4.95–4.76 (m, 1 H, OC*H*O-Et(CH_2Br)), 4.46 (s, 2 H, OCH_2Ph), 4.37–4.21 (m, 1 H, C*H*OH-alkyne), 3.83–3.27 (m, 6 H, OEt, CH_2OBn and CH_2Br), 2.39 (d, J = 2.0 Hz, 1 H, alkyne-H), 1.80–1.18 (m, 13 H, $(CH_2)_5$ and Me) ppm. IR (neat): $\tilde{\nu}$ = 2931, 2858, 1631, 1109, 1025, 751, 695 cm^{-1}. HRMS (ESI): calcd for $C_{20}H_{29}BrO_3Na$ [M + Na]$^+$ 419.1197; found 419.1203.

(2*S*)-2-[6-(Benzyloxy)hexyl]-5-ethoxy-3-methylenetetrahydrofuran (11): *n*Bu_3SnH (4.8 mL, 18.0 mmol) was added dropwise to a solution of bromoacetal **10a** (4.76 g, 12.05 mmol) heated to reflux in anhydrous benzene (40 mL) with catalytic AIBN under an N_2 atmosphere. The reduction was complete within 30 min as indicated by TLC analysis. Benzene was removed under reduced pressure and the crude residue was charged on a silica gel column, which was first eluted first with petroleum ether to remove excess tri-*n*Bu-tin hydride and *n*Bu_3SnBr formed in the reaction. The product was eluted with ethyl acetate/hexane (5%) to obtain the lactol ether **11** (3.45 g, 90%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 5 H, PhH), 5.12–5.03 (m, 1 H, C=CH_2), 5.00–4.94 (m, 1 H, C=CH_2), 4,86–4.81 (m, 1 H, OCHOEt), 4.47 (s, 2 H, OCH_2Ph), 4.44–4.24 (m, 1 H, CHOCHOEt), 3.80–3.64 (m, 1 H, OEt), 3.48–3.35 (m, 3 H, OEt and CH_2OBn), 2.83–2.42 (m, 2 H, Allylic-CH_2), 1.68–1.11 (m, 13 H, $(CH_2)_5$ and CH_3) ppm. IR (neat): $\tilde{\nu}$ = 2928, 2856, 1631, 1454, 1382, 1096, 1024, 987, 757, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{30}O_3Na$ [M + Na]$^+$ 341.2092; found 341.2086.

(*S*)-2-[6-(Benzyloxy)hexyl]-5-ethoxy-3-methyltetrahydrofuran (11a): Homoallylic lactol ether **11** (3.44 g, 10.82 mmol) and $NiCl_2{\cdot}6H_2O$ (0.26 g, 10.80 mmol) were dissolved in MeOH (40 mL). The reaction mixture was cooled to 0 °C and $NaBH_4$ (0.82 g, 37.63 mmol) was added in small portions (the solution turned black). After complete addition, the reaction mixture was stirred at r.t. for 1 h. The black precipitate formed was filtered and washed with MeOH and the methanol was removed under reduced pressure. To the residual

solution, water (20 mL) was added and the solution was extracted with diethyl ether (2 × 30 mL). The combined organic layers were washed with water (20 mL), brine (20 mL), dried with Na_2SO_4 and concentration under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 1:9) to afford a mixture of lactol ethers **11a** (3.11 g, 90%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.32–7.19 (m, 5 H, PhH), 5.07–4.98 (m, 1 H, OC*H*OEt), 4.46 (s, 2 H, OCH_2Ph), 3.96–3.60 (m, 2 H, OEt and CHOCHOEt), 3.48–3.28 (m, 3 H, OEt and CH_2OBn), 2.37–0.82 (m, 19 H, $(CH_2)_6CHCH_3$ and $(CH_3)_2$) ppm. IR (neat): $\tilde{\nu}$ = 2932, 2855, 1454, 1369, 1109, 983, 737, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{32}NaO_3$ [M + Na]$^+$ 343.2249; found 343.2247.

(4*S*,5*S*)-5-[6-(Benzyloxy)hexyl]-4-methyltetrahydrofuran-2-one (12-*syn*) and (4*R*,5*S*)-5-[6-(Benzyloxy)hexyl]-4-methyltetrahydrofuran-2-one (12-*anti*): Freshly prepared Jones reagent was added dropwise to the solution of lactol ethers **11a** (3.11 g, 9.73 mmol) in 2-propanol-free acetone (20 mL) at 0 °C until the color of the reagent persisted. The resulting mixture was then stirred at r.t. for 1 h. After completion of the reaction (monitored by TLC), excess reagent was quenched by the addition of 2-propanol and acetone was evaporated. Water (20 mL) was added and the mixture was extracted with diethyl ether (2 × 20 mL). The combined organic layers were washed with water (10 mL), brine (10 mL), dried with anhydrous Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (ethyl acetate/hexane, 1:9) to afford the *syn*-lactone **12**-*syn* (2.0 g) and the *anti*-lactone **12**-*anti* (0.5 g) in 4:1 ratio as colorless liquids (2.5 g, 88%).

12-*syn*-Lactone: $[\alpha]_D^{25}$ = –31.5 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H, PhH), 4.46 (s, 2 H, OCH_2Ph), 4.41–4.31 (m, 1 H, $CHOCOCH_2$), 3.42 (t, *J* = 6.5 Hz, 2 H, CH_2OBn), 2.63 (dd, *J* = 16.6, 7.5 Hz, 1 H, $CHOCOCH_2$), 2.57–2.47 (m, 1 H, C*H*CH_3), 2.13 (dd, *J* = 16.6, 3.7 Hz, 1 H, C*H*O-$COCH_2$), 1.69–1.23 (m, 10 H, $(CH_2)_5$), 1.00 (d, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8, 138.6, 128.3, 127.5, 127.4, 83.5, 72.8, 70.2, 37.5, 32.9, 29.8, 29.6, 29.2, 26.0, 25.8, 13.8 ppm. IR (neat): $\tilde{\nu}$ = 2930, 2855, 1774, 1631, 1456, 1384, 1161, 1100, 931, 737, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{26}NaO_3$ [M + Na]$^+$ 313.1779; found 313.1786.

12-*anti*-Lactone: $[\alpha]_D^{25}$ = –34.0 (*c* = 1.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 5 H, PhH), 4.46 (s, 2 H, OCH_2Ph), 3.98–3.90 (m, 1 H, C*H*O$COCH_2$), 3.43 (t, *J* = 6.5 Hz, 2 H, C*H*$_2$OBn), 2.69–2.52 (m, 1 H, $CHOCOCH_2$), 2.32–2.06 (m, 2 H, C*H*CH_3 and CH_2COOR), 1.70–1.23 (m, 9 H, CH_2COOR and $(CH_2)_4$), 1.13 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.6, 138.5, 128.3, 127.5, 127.4, 87.3, 72.8, 70.2, 37.0, 36.0, 33.9, 29.6, 29.1, 26.0, 25.6, 17.4 ppm.

(4*S*,5*S*)-5-[6-(Benzyloxy)hexyl]-4-methyltetrahydrofuran-2-ol (12a): DIBAL-H (1.0 M in hexane, 5.5 mL, 5.5 mmol) was added to a stirred solution of **12**-*syn*-lactone (1.6 g, 5.5 mmol) in CH_2Cl_2 (60 mL) at –78 °C and the solution was stirred for 1 h at the same temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched by addition of saturated potassium sodium tartrate (6 mL) and allowed to warm to ambient temperature. The aqueous phase was extracted with CH_2Cl_2 (2 × 40 mL), and the combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/hexane, 1.5:8.5) to afford lactol **12a** (1.56 g, 95%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.17 (m, 5 H, PhH), 5.50–5.32 (m, 1 H, OC*H*OH), 4.46 (s, 2 H, OC*H*$_2$Ph), 4.12–3.79 (m, 1 H, CHOCHOH), 3.42 (t, *J* = 6.5 Hz, 2 H, CH_2OBn), 3.22–2.93 (m, 1 H, OH), 2.42–2.14 (m, 1 H, CH_2CHOH), 2.03–1.92 (m, 1 H, C*H*CH_3), 1.78–1.23 (m, 11 H, $(CH_2)_5$ and CH_2CHOH), 1.04, 0.88 (2 × d, *J* = 6.8, 7.5 Hz, 3 H) ppm. IR (neat): $\tilde{\nu}$ = 3412, 2931, 2857, 1455, 1361, 1103, 987, 737, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{28}NaO_3$ [M + Na]$^+$ 315.1936; found 315.1928.

6-[(2*S*,3*S*,5*S*)-5-Allyl-3-methyltetrahydro-2-furanyl]-1-hexanol (13): A solution of lactol **12a** (1.26 g, 4.33 mmol) and allyltrimethylsilane (2.1 mL, 13.01 mmol) in CH_2Cl_2 (20 mL) was cooled to –78 °C. Freshly prepared 1 M solution of I_2 (0.2 mL, 5 mol-%, 0.22 mmol) in CH_2Cl_2 was added dropwise and the solution was stirred at –78 °C for 1 h and slowly brought to ambient temperature after completion of the allylation (monitored by TLC). An equivalent of molecular iodine was added to the reaction mixture (1.3 g, 4.34 mmol) at 0 °C and stirred for additional 1 h at the same temperature, then quenched with a saturated solution of $Na_2S_2O_3$ (10 mL). The layers were separated and the organic phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/hexane, 1.5:8.5) to afford **13** (0.85 g, 87%) as a colorless liquid (96:4 ratio determined by HPLC). $[\alpha]_D^{25}$ = +1.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.89–5.64 (m, 1 H, $CH{=}CH_2$), 5.11–4.97 (m, 2 H, $CH{=}CH_2$), 4.00–4.14 (m, 1 H, OCH-Allyl), 3.87–3.74 (m, 1 H, CHOCH-Allyl), 3.61 (t, *J* = 6.6 Hz, 2 H, CH_2OH), 2.40–2.04 (m, 3 H, CH_2CH-Allyl and Allylic-CH_2), 1.84–1.17 (m, 12 H, CH_2CH-Allyl, $CHCH_3$ and $(CH_2)_5$), 0.90 (d, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.8, 116.5, 81.3, 75.6, 62.6, 40.8, 39.1, 35.7, 32.4, 30.2, 29.4, 26.4, 25.5, 13.7 ppm. IR (neat): $\tilde{\nu}$ = 3410, 2930, 2858, 1641, 1458, 1375, 1057, 996, 913, 758 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{26}NaO_2$ [M + Na]$^+$ 249.1830; found 249.1829.

6-[(2*S*,3*S*,5*S*)-5-Allyl-3-methyltetrahydrofuran-2-yl]hexanoic Acid (13a): To a vigorously stirred solution of alcohol **13** (0.69 g, 3.0 mmol) in CH_3CN (6 mL) and H_2O (3 mL) were added TEMPO (95 mg, 0.61 mmol) and BAIB (2.45 g, 7.63 mmol). Stirring was continued until TLC indicated complete conversion of the starting material. The reaction mixture was quenched by the addition of saturated $Na_2S_2O_3$ (5 mL). The mixture was then extracted with EtOAc (2 × 30 mL) and the combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane, 3:7) to afford the pure acid **13a** (697 mg, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = –4.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.90–5.63 (m, 1 H, $CH{=}CH_2$), 5.09–4.97 (m, 2 H, $CH{=}CH_2$), 4.01–4.15 (m, 1 H, OCH-Allyl), 3.87–3.76 (m, 1 H, CHOCH-Allyl), 2.40–2.05 (m, 6 H, CH_2COOH, Allylic-CH_2, CH_2CH-Allyl, and $CHCH_3$), 1.85–1.21 (m, 9 H, CH_2CH-Allyl and $(CH_2)_4$), 0.89 (d, *J* = 7.3 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 179.5, 134.9, 116.8, 81.2, 76.0, 40.9, 39.1, 35.8, 34.0, 30.0, 29.2, 26.1, 24.6, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 3435, 2931, 2860, 1709, 1459, 1226, 1091, 993, 913 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{24}NaO_3$ [M + Na]$^+$ 263.1623; found 263.1619.

(4*S*)-3,6-[(2*S*,3*S*,5*S*)-5-Allyl-3-methyl-tetrahydrofuran-2-yl]-hexanoyl-4-benzyl-1,3-oxazolan-2-one (14): To a stirred solution of acid **13a** (2.76 g, 11.48 mmol) in THF (40 mL) at –20 °C was added Et_3N (4.0 mL, 28.70 mmol) followed by pivaloyl chloride (1.4 mL, 11.48 mmol). After stirring for 1 h at –20 °C, LiCl (0.73 g, 17.22 mmol) followed by (*S*)-oxazolidinone (2.03 g, 11.48 mmol) were added at the same temperature, and stirring was continued for 1 h at –20 °C and then for 2 h at 0 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (20 mL) and extracted with EtOAc

(2 × 40 mL). The combined organic layers were washed with brine (40 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane, 1.5:8.5) to afford **14** (3.90 g, 85%) as a colorless liquid. $[\alpha]_D^{25}$ = +34.3 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37–7.14 (m, 5 H, PhH), 5.89–5.63 (m, 1 H, CH=CH_2), 5.05 (d, *J* = 7.9, Hz, 1 H, CH=CH_2), 4.98 (s, 1 H, CH=CH_2), 4.68–4.54 (m, 1 H, NCOOCH_2), 4.22–3.99 (m, 2 H, NCOOCH_2, OCH-Allyl), 3.87–3.76 (m, 1 H, CHOCH-Allyl), 3.31 (dd, *J* = 3.5, 12.9 Hz, 1 H, NCHBn), 3.05–2.51 (m, 3 H, CH_2Ph and Allylic-CH_2), 2.39–2.0 (m, 4 H, Allylic-CH_2, CH_2CON and C*H*CH_3), 1.84–1.20 (m, 10 H, $(CH_2)_5$), 0.90 (d, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.2, 153.3, 135.1, 134.9, 129.2, 128.8, 127.1, 116.6, 81.0, 75.8, 66.0, 55.0, 40.8, 39.1, 37.8, 35.7, 35.3, 30.0, 29.1, 26.2, 24.0, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2934, 2865, 1782, 1702, 1383, 1212, 1093, 704 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{34}NO_4$ [M + H]$^+$ 400.2487; found 400.2472.

(4*S*)-3-(2*S*)-6-[(2*S*,3*S*,5*S*)-5-Allyl-3-methyltetrahydrofuran-2-yl]-2-methylhexanoyl-4-benzyl-1,3-oxazolan-2-one (14a): To a stirred solution of **14** (1.94 g, 4.85 mmol) in anhydrous THF (20 mL) at –78 °C, NaHMDS (1 M in THF, 7.28 mL, 7.28 mmol) was added dropwise under a nitrogen atmosphere. After stirring for 30 min at –78 °C, MeI (0.94 mL, 14.56 mmol) was added and the reaction mixture was stirred for an additional 3 h at –78 °C. Upon completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated NH_4Cl (20 mL), warmed to r.t. and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane, 1.3:8.7) to afford **14a** (1.60 g, 80%) as a colorless liquid. $[\alpha]_D^{25}$ = +44.7 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.36–7.15 (m, 5 H, PhH), 5.86–5.67 (m, 1 H, CH=CH_2), 5.08–4.97 (m, 2 H, CH=CH_2), 4.67–4.57 (m, 1 H, NCOOCH_2), 4.22–4.0 (m, 2 H, NCOOCH_2, OCH-Allyl), 3.84–3.61 (m, 1 H, CHOCH-Allyl), 3.28 (dd, *J* = 3.0, 13.6 Hz, 1 H, NCHBn), 2.70 (dd, *J* = 9.8, 12.8 Hz, 1 H, CH_2Ph), 2.34–2.09 (m, 3 H, CH_2Ph, NCOC*H*CH_3 and CH_2C*H*=CH_2), 1.79–1.62 (m, 2 H, CH_2C*H*=CH_2 and C*H*CH_3), 1.48–1.24 (m, 10 H, $(CH_2)_5$), 1.20 (d, *J* = 6.8 Hz, 3 H, CHC*H*$_3$), 0.89 (d, *J* = 7.5 Hz, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.3, 152.9, 135.3, 135.0, 129.4, 128.9, 127.2, 116.7, 81.2, 75.9, 65.9, 55.3, 41.0, 39.2, 37.9, 37.6, 35.8, 33.3, 30.2, 27.4, 26.6, 17.3, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2933, 2862, 1783, 1701, 1385, 1211, 1095, 703 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{35}NO_4Na$ [M + Na]$^+$ 436.2463; found 436.2465.

(2*S*)-6-[(2*S*,3*S*,5*S*)-5-Allyl-3-methyltetrahydrofuran-2-yl]-2-methylhexan-1-ol (15): To a solution of compound **14a** (1.6 g, 3.87 mmol) in anhydrous diethyl ether (20 mL) at 0 °C, was added one drop of distilled water followed portion-wise by $LiBH_4$ (0.17 g, 7.74 mmol), and stirring was continued until TLC analysis indicated complete conversion of the starting material. The reaction was quenched with saturated aqueous NH_4Cl (20 mL) and extracted with diethyl ether (2 × 50 mL). The combined organic extract was washed with brine (50 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane, 1:4) to afford **15** (798 mg, 86%) as a colorless liquid. $[\alpha]_D^{25}$ = –6.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.88–5.65 (m, 1 H, CH=CH_2), 5.06 (d, *J* = 8.1 Hz, 1 H, CH=CH_2), 4.99 (s, 1 H, CH=CH_2), 4.01–4.15 (m, 1 H, OCH-Allyl), 3.87–3.76 (m, 1 H, CHOCH-Allyl), 3.53–3.33 (m, 2 H, CH_2OH), 2.40–2.04 (m, 5 H, CH_2CH-Allyl, CH_2CH=CH_2 and C*H*CH_3), 1.85–0.99 (m, 9 H, C*H*CH_3, $(CH_2)_4$), 0.92 (d, *J* = 2.2 Hz, 3 H, C*H*CH_3), 0.89 (d, *J* = 2.2 Hz, 3 H, CHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 134.9, 116.7, 81.3, 76.0, 68.2, 41.0, 39.2, 35.8, 35.6, 33.0, 30.3, 27.1, 26.8, 16.5, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 3410, 2930, 2858, 1642, 1458, 1375, 1057, 996, 913 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{28}NaO_2$ [M + Na]$^+$ 263.1987; found 263.1980.

(*S*)-6-[(2*S*,3*S*,5*S*)-5-Allyl-3-methyltetrahydrofuran-2-yl]-2-methylhexyloxy-(*tert*-butyl)dimethylsilane (15a): To a stirred solution of alcohol **15** (3.9 g, 16.25 mmol) and imidazole (2.21 g, 32.5 mmol) in CH_2Cl_2 (50 mL), was added *tert*-butyldimethylsilyl chloride (TBDMSCl; 2.92 g, 19.50 mmol) at 0 °C portion-wise over a period of 10 min. The reaction mixture was stirred at r.t. for 3 h. After completion of the reaction (monitored by TLC), the mixture was then diluted with CH_2Cl_2 (50 mL) and washed with water (10 mL), brine (10 mL), and the organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by flash chromatography (ethyl acetate/hexane, 0.5:9.5) to afford TBS-protected alcohol **15a** (5.465 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ = –1.7 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.90–5.65 (m, 1 H, CH=CH_2), 5.12–4.97 (m, 2 H, CH=CH_2), 4.00–4.14 (m, 1 H, OCH-Allyl), 3.86–3.76 (m, 1 H, CHOCH-Allyl), 3.47–3.28 (m, 2 H, CH_2OTBS), 2.40–2.09 (m, 3 H, $CHCH_3$ and Allylic-CH_2), 1.83–1.18 (m, 11 H, $CHCH_3$ and $(CH_2)_5$), 0.93–0.83 (m, 15 H, OTBS and 2 × $CHCH_3$), 0.03 (s, 6 H, OTBS) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.0, 116.6, 81.4, 75.9, 68.4, 41.0, 39.3, 35.9, 35.7, 33.1, 30.4, 27.2, 26.9, 26.0, 18.3, 16.7, 14.0, –5.4 ppm. IR (neat): $\tilde{\nu}$ = 2930, 2858, 1642, 1458, 1375, 1057, 996, 913, 772 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{42}NaO_2Si$ [M + Na]$^+$ 377.2851; found 377.2838.

Compound 16: To a stirred solution of **15a** (5.4 g, 15.25 mmol) in THF (50 mL) and H_2O (6 mL) was added OsO_4 (106 mg, 0.76 mmol), and then NMO (1.96 g, 16.78 mmol) at r.t. The resulting brown solution was stirred until TLC indicated complete conversion of the starting material. The reaction mixture was diluted with diethyl ether (40 mL) and saturated $NaHCO_3$ (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 60 mL). The combined organic layers were washed with brine (50 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was used for the next step without further purification.

To a stirred solution of diol **15b** in THF (20 mL), and H_2O (20 mL), was added $NaIO_4$ (3.90 g, 18.30 mmol) at 23 °C under an open atmosphere. After 1 h at the same temperature, the resulting reaction mixture was diluted with diethyl ether (20 mL) and H_2O (20 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with H_2O (50 mL), brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude aldehyde was purified by flash chromatography (ethyl acetate/hexane, 1:9) to afford compound **16** (4.10 g, 76%) as a colorless oil. $[\alpha]_D^{25}$ = –3.5 (*c* = 1.6, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.78 (s, 1 H, CHO), 4.57–4.40 (m, 1 H, OCHCH_2CHO), 3.91–3.79 (m, 1 H, CHOCHCH_2CHO), 3.48–3.29 (m, 2 H, CH_2OTBS), 2.70–2.41 (m, 2 H, CH_2CHO), 2.38–2.16 (m, 1 H, $CHCH_3$), 1.94–1.66 (m, 2 H, CH_2CHCH_2CHO), 1.64–0.98 (m, 9 H, $CHCH_3$ and $(CH_2)_4$), 0.96–0.83 (m, 15 H, OTBS and 2 × CH_3), 0.02 (s, 6 H, OTBS) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.6, 81.7, 71.6, 68.5, 50.5, 40.0, 35.7, 35.8, 33.1, 30.3, 27.2, 26.8, 25.9, 18.4, 16.7, 13.8, –5.4 ppm. IR (neat): $\tilde{\nu}$ = 2930, 2858, 1729, 1458, 1375, 1057, 996, 913, 772 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{40}O_3NaSi$ [M + Na]$^+$ 379.2644; found 379.2656.

Compound 16a: Sodium borohydride (424 mg, 11.23 mmol) was added portion-wise to a cooled solution (0 °C) of aldehyde **16** (4.0 g, 11.23 mmol) in MeOH (30 mL). The solution was stirred for

1 h at r.t., then the reaction was quenched by the addition of saturated NH_4Cl (10 mL) and methanol was concentrated. The aqueous phase was extracted with EtOAc (2 × 50 mL) and the combined organic layers were washed with brine (50 mL), dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane, 2:8) to afford alcohol **16a** (3.82 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ = –7.4 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.32–4.20 (m, 1 H, $OCHCH_2CH_2OH$), 3.93–3.73 (m, 3 H, CH_2OTBS and $CHOCHCH_2CH_2OH$), 3.43 (dd, *J* = 9.8, 5.8 Hz, 1 H, CH_2OH), 3.34 (dd, *J* = 9.8, 6.6 Hz, 1 H, CH_2OH), 3.2 (br. s, 1 H, OH), 2.28–2.15 (m, 1 H, $CHCH_3$), 1.83–1.20 (m, 12 H, $CHCH_3$, CH_2CH_2OH and $(CH_2)_5$), 1.12–0.98 (m, 1 H, CH_2CH_2OH), 0.91–0.83 (m, 15 H, OTBS and 2 × CH_3), 0.03 (s, 6 H, OTBS) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 81.4, 77.2, 68.4, 62.0, 40.5, 38.0, 35.7, 35.6, 33.0, 30.4, 27.2, 26.9, 25.9, 18.3, 16.7, 14.0, –5.4 ppm. IR (neat): $\tilde{\nu}$ = 3426, 2857, 1465, 1253, 1093, 839, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{42}NaO_3Si$ [M + Na]$^+$ 381.2800; found 381.2805.

((*S*)-6-{(2*S*,3*S*,5*R*)-5-[2-(4-Methoxybenzyloxy)ethyl]-3-methyltetrahydrofuran-2-yl}-2-methylhexyloxy)(*tert*-butyl)dimethylsilane (17): To a stirred suspension of NaH (60%, 0.61 g, 15.92 mmol) in THF (20 mL) was added a solution of mono-protected alcohol **16a** (3.80 g, 10.61 mmol) in anhydrous THF (20 mL) dropwise over a period of 10 min at 0 °C. The reaction mixture was stirred at r.t. for 1 h, then freshly prepared *p*-methoxybenzyl bromide (3.2 g, 15.92 mmol) dissolved in THF (10 mL) was added at 0 °C over a period of 10 min, followed by addition of TBAI (0.195 g, 0.53 mmol) and the reaction mixture was stirred at r.t. until TLC indicated complete conversion of the starting material. The reaction mixture was quenched by addition of cold water (10 mL) and THF was removed under reduced pressure. The crude mixture was extracted with ethyl acetate (2 × 20 mL) and the combined organic layer was washed with brine (10 mL) and dried with anhydrous Na_2SO_4. Concentration under reduced pressure and purification by silica gel column chromatography (ethyl acetate/hexane, 0.5:9.5) afforded *p*-methoxybenzyl ether **17** (4.05 g, 80%) as a colorless liquid. $[\alpha]_D^{25}$ = –7.8 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.8 Hz, 2 H, $CH_3OC_6H_4$), 6.86 (d, *J* = 8.8 Hz, 2 H, $CH_3OC_6H_4$), 4.49–4.38 (m, 2 H, $OCH_2C_6H_4OCH_3$), 4.22–4.10 (m, 1 H, $OCHCH_2CH_2OPMB$), 3.80 (s, 3 H, OCH_3), 3.58–3.51 (m, 2 H, CH_2OPMB and $CHOCHCH_2CH_2OPMB$), 3.44 (dd, *J* = 9.8, 5.8 Hz, 1 H, CH_2OTBS), 3.34 (dd, *J* = 9.8, 6.6 Hz, 1 H, CH_2OTBS), 2.25–2.15 (m, 1 H, $CHCH_3$), 1.92–1.66 (m, 3 H, $CHCH_3$ and $CH_2CHCH_2CH_2OPMB$), 1.63–1.21 (m, 10 H, CH_2CH_2OPMB and $(CH_2)_4$), 1.11–0.96 (m, 1 H, CH_2CH_2OTBS), 0.92–0.84 (m, 15 H, OTBS and 2 × CH_3), 0.03 (s, 6 H, OTBS) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 129.4, 129.2, 113.7, 80.9, 73.9, 72.6, 68.4, 67.6, 55.2, 40.1, 36.9, 35.8, 35.7, 33.1, 30.4, 27.2, 26.9, 25.9, 18.3, 16.7, 13.9, –5.37 ppm. IR (neat): $\tilde{\nu}$ = 2930, 2856, 1612, 1513, 1463, 1248, 1093, 1037, 838, 775 cm^{-1}. HRMS (ESI): calcd. for $C_{28}H_{50}NaO_4Si$ [M + Na]$^+$ 501.3376; found 501.3383.

(*S*)-6-{(2*S*,3*S*,5*R*)-5-[2-(4-Methoxybenzyloxy)ethyl]-3-methyltetrahydrofuran-2-yl}-2-methylhexan-1-ol (17a): To a solution of compound **17** (4.0 g, 8.37 mmol) in THF (30 mL), was added 70% HF·Py complex (4.96 mL, 10.87 mmol) at r.t. The reaction mixture was stirred until TLC indicated complete conversion of the starting material. The reaction mixture was then quenched with ice-water (6 mL) and the resulting mixture was diluted with diethyl ether (30 mL). The organic layer was separated and the aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layers were successively washed with water (50 mL) and brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated. The residue was purified by flash chromatography (ethyl acetate/hexane, 1:9) to afford compound **17a** (2.83 g, 93%) as a colorless oil. $[\alpha]_D^{25}$ = –12.9 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2 H, $CH_3OC_6H_4$), 6.87 (d, *J* = 8.7 Hz, 2 H, $CH_3OC_6H_4$), 4.40 (ABq, *J* = 11.5, 15.1 Hz, 2 H, $OCH_2C_6H_4OCH_3$), 4.22–4.11 (m, 1 H, $OCHCH_2CH_2OPMB$), 3.85–3.77 (m, 4 H, OCH_3 and $CHOCHCH_2CH_2OPMB$), 3.59–3.37 (m, 4 H, CH_2OPMB and CH_2OH), 2.27–2.14 (m, 1 H, $CHCH_3$), 1.91–1.05 (m, 13 H, $(CH_2)_6$ and $CHCH_3$), 0.93–0.87 (m, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.0, 130.5, 129.1, 113.6, 80.9, 73.8, 72.5, 68.0, 67.5, 55.1, 40.0, 36.7, 35.7, 35.6, 33.0, 30.2, 27.0, 26.8, 16.5, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 3436, 2932, 2860, 1613, 1513, 1460, 1247, 1091, 1037, 821, 756 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{36}NaO_4$ [M + Na]$^+$ 387.2511; found 387.2519.

(*S*)-6-{(2*S*,3*S*,5*R*)-5-[2-(4-Methoxybenzyloxy)ethyl]-3-methyltetrahydrofuran-2-yl}-2-methylhexanoic Acid (4): To a vigorously stirred solution of alcohol **17a** (2.8 g, 7.69 mmol) in CH_2Cl_2 (15 mL) and H_2O (7 mL), was added TEMPO (0.24 g, 1.54 mmol) and BAIB (6.2 g, 19.23 mmol). Stirring was continued until TLC indicated complete conversion of the starting material. The reaction mixture was quenched by the addition of saturated $Na_2S_2O_3$ (50 mL), the mixture was extracted with EtOAc (2 × 100 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/hexane, 1:4) to afford the pure acid **4** (2.76 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = –2.1 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (d, *J* = 8.7 Hz, 2 H, $CH_3OC_6H_4$), 6.87 (d, *J* = 8.7 Hz, 2 H, $CH_3OC_6H_4$), 4.43 (ABq, *J* = 11.5, 3.6 Hz, 2 H, $OCH_2C_6H_4OCH_3$), 4.22–4.11 (m, 1 H, $OCHCH_2CH_2OPMB$), 3.85–3.77 (m, 4 H, OCH_3 and $CHOCHCH_2CH_2OPMB$), 3.54 (t, *J* = 6.6 Hz, 2 H, CH_2OPMB), 2.52–2.37 (m, 1 H, CHCOOH), 2.27–2.14 (m, 1 H, $CHCH_3$), 1.89–1.62 (m, 3 H, $CHCH_2CH$, CH_2), 1.51–1.24 (m, 9 H, $CHCH_2CH$, $(CH_2)_4$), 1.17 (d, *J* = 7.0 Hz, 3 H, CH_3), 0.88 (d, *J* = 7.1 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.3, 158.9, 130.4, 129.2, 113.6, 80.8, 73.8, 72.5, 67.3, 55.2, 39.9, 39.4, 36.6, 35.6, 33.5, 30.0, 27.2, 26.3, 16.8, 13.8 ppm. IR (neat): $\tilde{\nu}$ = 2924, 2854, 1695, 1513, 1460, 1247, 1091, 1037, 821, 756 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{34}NaO_5$ [M + Na]$^+$ 401.2304; found 401.2315.

1-[((*S*)-3-Iodo-2-methylpropoxy)methyl]benzene (7a): To a stirred solution of mono-benzyl ether **7** (20.0 g, 111.1 mmol) in a mixture of anhydrous diethyl ether (150 mL) and anhydrous CH_3CN (50 mL), was added triphenylphosphane (TPP; 57.99 g, 222.2 mmol), imidazole (22.69 g, 333.3 mmol), and iodine (56.44 g, 222.2 mmol) at 0 °C. The resulting mixture was stirred at r.t. for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with hexane and the solid material was filtered and washed with ethyl acetate/hexane (10%). The filtrate was concentrated under reduced pressure and the crude product was dissolved in diethyl ether (100 mL) and washed with aqueous sodium thiosulphate (10%, 75 mL), brine (75 mL) and dried with Na_2SO_4. Concentration under reduced pressure and purification by silica gel column chromatography (ethyl acetate/hexane, 0.3:9.7) afforded the iodo-compound **7a** (29 g, 90%) as a viscous liquid. $[\alpha]_D^{25}$ = +8.2 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35–7.20 (m, 5 H, C_6H_5), 4.48 (s, 2 H, OCH_2Ph), 3.42–3.19 (m, 4 H, CH_2OBn and CH_2I), 1.84–1.65 (m, 1 H, $CHCH_3$), 0.99 (d, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 138.2, 128.2, 127.3, 73.9, 73.0, 35.0, 17.5, 13.7 ppm. IR (neat): $\tilde{\nu}$ = 2858, 1642, 1454, 1099, 739, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}INaO$ [M + Na]$^+$ 313.0065; found 313.0059.

(*R*)-5-(Benzyloxy)-4-methyl-2-methylenepentan-1-ol (18): To a stirred solution of diethyl malonate (14.65 mL, 96.55 mmol) in an-

hydrous THF (100 mL) was added *n*BuLi (1.6 M in hexane), 60.34 mL, 96.55 mmol) at 0 °C. After 15 min, iodo-compound **7a** (28.0 g, 96.55 mmol) in anhydrous THF (50 mL) was added to the reaction mixture over a period of 10 min. The resulting mixture was stirred at r.t. for 4 h. After completion of the reaction (monitored by TLC), *n*BuLi (1.6 M in hexane), 60.34 mL, 96.55 mmol) was added at 0 °C. After 15 min the reaction mixture was transferred by using a cannula into a separately generated alane complex [To a stirred suspension of $LiAlH_4$ (11.0 g, 289.65 mmol) in anhydrous THF (200 mL) at 0 °C under an N_2 atmosphere, was added dropwise a solution of $AlCl_3$ (12.87 g, 96.55 mmol) in THF (100 mL)]. The reaction mixture was stirred at reflux temperature for 6 h. After completion (reaction monitored by TLC), the reaction mixture was quenched by the addition of crushed ice, filtered through Celite and washed with hot ethyl acetate. The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (ethyl acetate/hexane, 1:9) afforded allyl alcohol **18** (12.76 g, 60%) as a viscous liquid. $[\alpha]_D^{25}$ = –0.6 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.34–7.20 (m, 5 H, C_6H_5), 5.09 (s, 1 H, C=CH_2), 4.81 (s, 1 H, C=CH_2), 4.45 (s, 2 H, OCH_2Ph), 3.97 (s, 2 H, CH_2=CCH_2OH), 3.27 (d, *J* = 6.0 Hz, 2 H, CH_2OBn), 2.25 (dd, *J* = 13.6, 6.0 Hz, 1 H, CH_2=CCH_2), 2.13 (br. s, 1 H, OH), 2.02–1.79 (m, 2 H, CH_2=CCH_2 and $CHCH_3$), 0.91 (d, *J* = 6.8 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 147.1, 138.3, 128.2, 127.4, 127.4, 110.7, 75.4, 72.9, 65.4, 37.5, 31.7, 17.0 ppm. IR (neat): $\tilde{\nu}$ = 3425, 2923, 2860, 1647, 1454, 1094, 739, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{20}NaO_2$ $[M + Na]^+$ 243.1361; found 243.1368.

1-{[(*R*)-4-(Bromomethyl)-2-methylpent-4-enyloxy]methyl}benzene (18a): To a solution of CBr_4 (19.16 g, 57.72 mmol) in anhydrous CH_2Cl_2 (100 mL) under a nitrogen atmosphere, was added a solution of TPP (30.13 g, 115.44 mmol) in anhydrous CH_2Cl_2 (100 mL) dropwise over a period of 30 min at 0 °C. The mixture was stirred for 30 min at 0 °C followed by the addition of allylic alcohol **18** (12.7 g, 57.72 mmol) and imidazole (7.4 g, 115.44 mmol) in anhydrous CH_2Cl_2 (50 mL). The reaction mixture was allowed to warm to r.t., then the solvent was evaporated to a small volume and hexane was added to the reaction mixture. The resultant precipitate was filtered and washed with ethyl acetate/hexane (10%). The filtrate was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 0.5:9.5) to afford **18a** (14.71 g, 90%) as a colorless liquid. $[\alpha]_D^{25}$ = –2.0 (*c* = 2.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 5 H, C_6H_5), 5.19 (s, 1 H, C=CH_2), 4.93 (s, 1 H, C=CH_2), 4.47 (s, 2 H, OCH_2Ph), 3.92 (s, 2 H, CH_2=CCH_2Br), 3.28 (dd, *J* = 2.2, 5.1 Hz, 2 H, CH_2OBn), 2.49–2.32 (m, 1 H, CH_2=CCH_2), 2.08–1.91 (m, 2 H, CH_2=CCH_2 and $CHCH_3$), 0.94 (d, *J* = 6.6 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.8, 138.6, 128.3, 127.5, 127.4, 116.5, 75.3, 73.0, 37.8, 36.6, 31.5, 17.0 ppm. IR (neat): $\tilde{\nu}$ = 2923, 2855, 1638, 1455, 1207, 1111, 740, 696, 541 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{19}BrNaO$ $[M + Na]^+$ 305.0517; found 305.0520.

(*R*)-8-[(Benzyloxy)methyl]-6-methylenenonan-4-ol (19): To a stirred mixture of activated Zn (33.65 g, 517.73 mmol) in THF (100 mL), was added **18a** (14.60 g, 51.77 mmol) in THF (50 mL) dropwise. After stirring for 1 h, butanal (13.9 mL, 155.32 mmol) was added and the reaction mixture was stirred for an additional 3 h at r.t. then quenched by addition of saturated aqueous NH_4Cl (100 mL). After 30 min, the reaction mixture was filtered to remove the excess zinc. The filtrate was acidified with 10% HCl (50 mL) and the organic layer was separated. The aqueous layer was extracted with diethyl ether (2 × 100 mL), the combined organic extracts were dried with Na_2SO_4, and concentrated under reduced pressure. Purification of the crude product by silica gel column chromatography (ethyl acetate/hexane, 0.8:9.2) afforded the homoallylic alcohol **19** (14.31 g, 76%) as a colorless liquid. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.21 (m, 5 H, C_6H_5), 4.86 (d, *J* = 3.0 Hz, 2 H, C=CH_2), 4.46 (d, *J* = 3.0 Hz, 2 H, OCH_2Ph), 3.74–3.60 (m, 1 H, CHOH), 3.31–3.21 (m, 2 H, CH_2OBn), 2.34–2.13 (m, 2 H, CH_2=CCH_2), 2.08–1.72 (m, 3 H, $CHCH_3$ and CH_2=CCH_2), 1.64 (br. s, 1 H, OH), 1.55–1.29 (m, 4 H, $(CH_2)_2$), 0.97–0.88 (m, 6 H, 2 × CH_3) ppm. IR (neat): $\tilde{\nu}$ = 3453, 2957, 2927, 2868, 1641, 1455, 1207, 1095, 737, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{28}NaO_2$ $[M + Na]^+$ 299.1987; found 299.1989.

(4*S*,8*R*)-9-(Benzyloxy)-8-methyl-6-methylenenonan-4-ol (20) and (4*S*,8*R*)-9-(Benzyloxy)-8-methyl-6-methylenenon-an-4-yl Acetate (21): To a solution of homoallylic alcohol **19** (14.3 g, 51.73 mmol) in diisopropyl ether (600 mL) was added vinyl acetate (13.5 mL, 155.19 mmol) and Lipase PS-C "Amano" II (2.59 g, or 0.1 mmol of alcohol, 5 mg enzyme) at r.t. After stirring for 4 d at r.t., the mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 0.5:9.5) to obtain the homoallylic acetate **21** (6.26 g, 38%; >98% *ee*) as a colorless liquid [the enantiomeric excess *ee* was measured by chiral HPLC using CHIRAL PAK-IC column. Eluent: hexane/IPA, 99:1; flow rate: 1.0 mL/min; 25 °C (λ_{max} = 210 nm)]. The unrequired alcohol **20** was converted into the required acetate **21** by an oxidation, reduction, followed by enzymatic resolution sequence.

Compound 21: $[\alpha]_D^{25}$ = +7.8 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.17 (m, 5 H, C_6H_5), 5.03–4.93 (m, 1 H, CHOAc), 4.77 (s, 2 H, C=CH_2), 4.47 (s, 2 H, OCH_2Ph), 3.33–3.19 (m, 2 H, CH_2OBn), 2.29–2.10 (m, 3 H, CH_2=CCH_2), 1.98 (s, 3 H, OAc), 1.87–1.76 (m, 1 H, CH_2=CCH_2), 1.54–1.41 (m, 3 H, $CHCH_3$ and CH_2), 1.39–1.23 (m, 2 H, CH_2), 0.95–0.87 (m, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 143.9, 138.6, 128.2, 127.5, 127.4, 113.6, 75.4, 72.9, 72.2, 40.6, 40.4, 36.1, 31.4, 21.2, 18.6, 17.1, 13.9 ppm. IR (neat): $\tilde{\nu}$ = 2959, 2929, 2870, 1737, 1456, 1371, 1241, 1096, 1022, 898, 738, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{20}H_{30}NaO_3$ $[M + Na]^+$ 341.2093; found 341.2097.

(4*R*,8*R*)-9-(Benzyloxy)-8-methyl-6-methylenenonan-4-ol (5): To a stirred solution of (*R*)-homoallylic ester **21** (6.2 g, 19.47 mmol) in MeOH (40 mL) was added Na metal (672 mg, 29.2 mmol) portionwise at 0 °C over a period of 10 min. The reaction mixture was stirred at r.t. for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was concentrated under reduced pressure. The crude product was dissolved in H_2O (30 mL) and extracted with diethyl ether (2 × 50 mL). The combined organic layer was washed with brine (50 mL), dried with Na_2SO_4, and purified by silica gel column chromatography (ethyl acetate/hexane, 0.8:9.2) to afford (*R*)-homoallylic alcohol **5** (5.10 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = +0.6 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.21 (m, 5 H, C_6H_5), 4.85 (s, 2 H, C=CH_2), 4.46 (s, 2 H, OCH_2Ph), 3.72–3.63 (m, 1 H, CHOH), 3.31–3.21 (m, 2 H, CH_2OBn), 2.24–2.14 (m, 2 H, CH_2=CCH_2), 2.07–1.80 (m, 3 H, $CHCH_3$ and CH_2=CCH_2), 1.63 (br. s, 1 H, OH), 1.56–1.31 (m, 4 H, $(CH_2)_2$), 0.96–0.90 (m, 6 H, 2 × CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0, 138.6, 128.3, 127.5, 127.4, 113.6, 75.3, 73.0, 68.7, 44.3, 40.5, 39.2, 31.7, 18.9, 17.4, 14.1 ppm. IR (neat): $\tilde{\nu}$ = 3435, 2957, 2927, 2868, 1641, 1455, 1365, 1095, 1022, 895, 737, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{28}NaO_2$ $[M + Na]^+$ 299.1987; found 299.1989.

(4*R*,8*R*)-9-(Benzyloxy)-8-methyl-6-methylenenonan-4-yloxy(*tert*-butyl)dimethylsilane (24): To a stirred solution of (*R*)-homoallylic

alcohol **5** (2.6 g, 9.42 mmol) and imidazole (1.6 g, 23.55 mmol) in CH_2Cl_2 (20 mL), was added a solution of TBDMS-Cl (1.69 g, 11.30 mmol) in CH_2Cl_2 (5 mL) at 0 °C over a period of 10 min. The reaction mixture was stirred at r.t. for 3 h. Upon completion of the reaction (monitored by TLC), the mixture was diluted with CH_2Cl_2 (50 mL) and washed with water (40 mL) and brine (40 mL). The organic layer was dried with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane, 0.3:9.7) to afford TBS-protected alcohol **24** (3.34 g, 91%) as a colorless oil. $[\alpha]_D^{25}$ = –1.4 (*c* = 1.5, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.34–7.24 (m, 5 H, C_6H_5), 4.76 (d, *J* = 2.2 Hz, 2 H, C=CH_2), 4.48 (s, 2 H, OCH_2Ph), 3.85–3.71 (m, 1 H, CHOTBS), 3.27 (d, *J* = 5.8 Hz, 2 H, CH_2OBn), 2.30–1.59 (m, 5 H, 2 × CH_2=CCH_2 and $CHCH_3$), 1.51–1.14 (m, 4 H, $(CH_2)_2$), 0.96–0.85 (m, 15 H, OTBS and 2 × CH_3), 0.04 (s, 6 H, OTBS) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.9, 138.8, 128.3, 127.4, 127.4, 113.3, 75.6, 72.9, 70.8, 43.9, 40.8, 39.0, 31.6, 26.0, 18.5, 18.1, 17.0, 14.2, –4.4, –4.5 ppm. IR (neat): $\tilde{\nu}$ = 2930, 2856, 1641, 1462, 1365, 1250, 1101, 1035, 830, 770, 735, 693 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{42}NaO_2Si$ $[M + Na]^+$ 413.2852; found 413.2845.

Compound 24a: To a stirred solution of naphthalene (4.33 g, 33.84 mmol) in THF (30 mL) was added lithium metal (177 mg, 25.38 mmol) in small pieces at r.t. The reaction mixture was stirred at r.t. under an argon atmosphere until the lithium metal was completely dissolved (3 h). The resulting dark-green solution of lithium naphthalenide was cooled to –20 °C and compound **24** (3.3 g, 8.46 mmol) in THF (6 mL) was added dropwise over 5 min. The resulting mixture was stirred at –20 °C for 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with aqueous ammonium chloride (6 mL). The resulting solution was extracted with diethyl ether (2 × 60 mL) and the combined extracts were washed with water and brine (10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by column chromatography (ethyl acetate/hexane, 0.9:9.1) to afford **24a** (2.41 g, 95%) as a colorless liquid. $[\alpha]_D^{25}$ = +15.5 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.79 (s, 2 H, C=CH_2), 3.85–3.69 (m, 1 H, CHOTBS), 3.45 (d, *J* = 5.3 Hz, 2 H, CH_2OH), 2.25–2.03 (m, 4 H, 2 × CH_2=CCH_2), 1.91–1.71 (m, 1 H, $CHCH_3$), 1.49–1.17 (m, 4 H, $(CH_2)_2$), 1.01–0.76 (m, 15 H, OTBS and 2 × CH_3), 0.04 (s, 6 H, OTBS) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.4, 113.4, 70.9, 68.2, 43.7, 40.7, 39.0, 33.8, 25.9, 18.5, 18.1, 16.7, 14.2, –4.4, –4.5 ppm. IR (neat): $\tilde{\nu}$ = 3421, 2956, 2930, 2858, 1641, 1464, 1252, 1038, 833, 772 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{36}O_2NaSi$ $[M + Na]^+$ 323.2382; found 323.2391.

Compound 25: To a vigorously stirred solution of alcohol **24a** (0.20 g, 0.66 mmol) in CH_2Cl_2 (6 mL) and H_2O (3 mL) was added TEMPO (21 mg, 0.13 mmol) and BAIB (536 mg, 1.66 mmol). Stirring was continued until TLC indicated complete conversion of the starting material. The reaction mixture was quenched by the addition of saturated $Na_2S_2O_3$ (25 mL) and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/hexane, 1:4) to afford the pure acid **25** (190 mg, 93%) as a colorless liquid. $[\alpha]_D^{25}$ = +3.0 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.83 (s, 2 H, C=CH_2), 3.83–3.73 (m, 1 H, CHOTBS), 2.73–2.60 (m, 1 H, CHCOOH), 2.46 (dd, *J* = 7.0, 14.4 Hz, 1 H, CH_2=CCH_2), 2.23–2.05 (m, 3 H, 2 × CH_2=CCH_2), 1.47–1.27 (m, 4 H, $(CH_2)_2$), 1.18 (d, *J* = 7.0 Hz, 3 H, $CHCH_3$), 0.91–0.85 (m, 12 H, CH_2CH_3 and OTBS), 0.05 (s, 3 H, OTBS), 0.04 (s, 3 H, OTBS) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.0, 146.7, 114.0, 70.9, 43.8, 40.2, 39.0, 37.7, 25.9, 18.5, 18.1, 16.7, 14.2, –4.4, –4.6 ppm. IR (neat): $\tilde{\nu}$ = 3423, 2956, 2930, 2858, 1709, 1463, 1252, 1040, 834, 772 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{34}O_3NaSi$ $[M + Na]^+$ 337.2175; found 337.2185.

(2*S*)-(4*R*,8*R*)-9-(Benzyloxy)-8-methyl-6-methylenenonan-4-yl 6-{(2*S*,3*S*,5*R*)-5-[2-(4-Methoxybenzyloxy)ethyl]tetrahydro-3-methylfuran-2-yl}-2-methylhexanoate (22): To a solution of acid **4** (2.70 g, 7.14 mmol) in toluene (25 mL) were added 2,4,6-trichlorobenzoyl chloride (1.67 mL, 10.71 mmol) and diisopropylethylamine (3.73 mL, 21.43 mmol). The mixture was stirred for 6 h at r.t., then alcohol **5** (2.168 g, 7.85 mmol) in toluene (5 mL) was slowly added to the mixture followed by addition of DMAP (1.3 g, 10.71 mmol) in toluene (5 mL) at r.t. The reaction was stirred for an additional 3 h. Upon completion of the reaction (monitored by TLC), it was quenched by addition of saturated aqueous NH_4Cl (50 mL). The aqueous phase was extracted with ethyl acetate (3 × 50 mL) and the combined extracts were washed with brine (30 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/hexane, 0.5:9.5) to afford compound **22** (3.86 g, 85%) as a colorless viscous liquid. $[\alpha]_D^{25}$ = +1.2 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.22 (m, 7 H, C_6H_5 and $C_6H_4OCH_3$), 6.87 (d, *J* = 8.7 Hz, 2 H, $C_6H_4OCH_3$), 5.08–4.97 (m, 1 H, CH-(CH_3)OCOR), 4.78 (d, *J* = 4.7 Hz, 2 H, C=CH_2), 4.50 (s, 2 H, OCH_2Ph), 4.43 (ABq, *J* = 11.5, 3.7 Hz, 2 H, $OCH_2C_6H_4OCH_3$), 4.21–4.10 (m, 1 H, $OCHCH_2CH_2OPMB$), 3.86–3.75 (m, 4 H, $OCHCH(CH_3)$ and OCH_3), 3.54 (t, *J* = 7.3 Hz, 2 H, CH_2OPMB), 3.38–3.32 (m, 1 H, CH_2OBn), 3.27–3.20 (m, 1 H, CH_2OBn), 2.44–2.11 (m, 5 H, 2 × Allylic-CH_2 and $CH(CH_3)COOR$), 2.08–1.81 (m, 2 H, $CHCH_3$ and $OCHCH_2$), 1.77–1.59 (m, 4 H, $CHCH_3$, $OCHCH_2CH_2OPMB$ and $OCHCH_2CH(CH_3)$), 1.56–1.21 (m, 12 H, $(CH_2)_6$), 1.10 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 0.95–0.86 (m, 9 H, 2 × $CHCH_3$, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.2, 158.9, 143.6, 138.5, 130.4, 129.0, 128.0, 127.2, 127.1, 113.5, 113.4, 80.6, 75.2, 73.7, 72.7, 72.4, 71.3, 67.4, 55.0, 40.6, 40.1, 40.0, 39.6, 36.7, 36.0, 35.6, 33.6, 31.2, 30.1, 27.3, 26.3, 18.4, 17.0, 13.8 ppm. IR (neat): $\tilde{\nu}$ = 2933, 2861, 1727, 1613, 1513, 1458, 1374, 1248, 1174, 1095, 1035, 899, 822, 739, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{40}H_{60}NaO_6$ $[M + Na]^+$ 659.4287; found 659.4282.

(2*S*)-(4*R*,8*R*)-9-Hydroxy-8-methyl-6-methylenenonan-4-yl 6-[(2*S*,3*S*,5*R*)-Tetrahydro-5-(2-hydroxyethyl)-3-methylfuran-2-yl]-2-methylhexanoate (3): DDQ (40.5 g, 179.24 mmol) was added to a solution of ester **22** (3.8 g, 5.97 mmol) in CH_2Cl_2/H_2O (590 mL, 10:1 v/v). The reaction mixture was stirred for 18 h at r.t. and quenched by addition of saturated aqueous $NaHCO_3$ (400 mL). The aqueous phase was extracted with diethyl ether (3 × 100 mL) and the combined extracts were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography (ethyl acetate/hexane, 4:6) to afford diol **3** (2.36 g, 93%) as a colorless oil. $[\alpha]_D^{25}$ = +11.4 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.03 (m, 1 H, $CHOCOCHCH_3$), 4.80 (s, 2 H, C=CH_2), 4.32–4.22 (m, 1 H, $OCHCH_2CH_2OH$), 3.92–3.74 (m, 3 H, CH_2CH_2OH and $OCHCHCH_3$), 3.52–3.41 (m, 2 H, $CH(CH_3)CH_2OH$), 2.44–2.13 (m, 6 H, 2 × Allylic-CH_2, $CH(CH_3)COOR$ and OH), 1.92–1.59 (m, 7 H, $(CH_2)_3$ and $CHCH_3$), 1.57–1.22 (m, 12 H, $(CH_2)_6$), 1.11 (d, *J* = 6.9 Hz, 3 H, $CHCH_3$), 0.94–0.88 (m, 9 H, 2 × $CHCH_3$, CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.8, 143.8, 113.5, 81.2, 76.9, 71.5, 67.5, 61.8, 41.0, 40.3, 39.7, 39.6, 38.0, 36.1, 35.5, 33.6, 33.4, 30.1, 27.3, 26.5, 18.5, 17.2, 16.7, 13.9, 13.8 ppm. IR (neat): $\tilde{\nu}$ = 3404, 2928, 2860, 1727, 1458, 1379, 1177, 1043,

897 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{46}NaO_5$ $[M + Na]^+$ 449.3242; found 449.3259.

Amphidinin B (2): To a vigorously stirred solution of diol **3** (2.3 g, 5.4 mmol) in CH_2Cl_2 (12 mL) and H_2O (6 mL) was added TEMPO (343 mg, 2.16 mmol) and BAIB (8.69 g, 26.99 mmol). Stirring was continued until TLC indicated complete conversion of the starting material. The reaction mixture was quenched by the addition of saturated $Na_2S_2O_3$ (40 mL), extracted with EtOAc (2 × 70 mL) and the combined organic layers were washed with brine (70 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography (ethyl acetate/hexane, 6:4) to afford **2** (2.2 g, 90%) as a colorless liquid. $[\alpha]_D^{25}$ = –7.6 (*c* = 0.7, $CHCl_3$). ^1H NMR (600 MHz, C_6D_6): δ = 5.29–5.24 (m, 1 H, RCOOCHR), 4.90 (s, 1 H, C=CH_2), 4.88 (s, 1 H, C=CH_2), 4.40–4.34 (m, 1 H, OCHCH_2), 3.69–3.65 (m, 1 H, OCHCH_3), 2.68–2.61 (m, 1 H, CH_3CHCOOH), 2.60–2.48 (m, 2 H, CH_2COOH and CH_2C=CH_2), 2.30–2.22 (m, 2 H, CH_2C=CH_2 and CH_2COOH), 2.09 (dd, *J* = 14.6, 4.3 Hz, 1 H, CH_2C=CH_2), 2.0 (dd, *J* = 14.6, 3.9 Hz, 1 H, CH_2C=CH_2), 1.93 (dd, *J* = 14.9, 6.1 Hz, 1 H, OCHCHCH_3), 1.82–1.75 (m, 2 H, OCHCH_2), 1.56–1.49 (m, 1 H, OCHCH_2), 1.46–1.27 (m, 12 H, $(CH_2)_6$), 1.20 (d, *J* = 6.7 Hz, 3 H, $CHCH_3$), 1.04 (d, *J* = 6.7 Hz, 3 H, $CHCH_3$), 0.87 (t, *J* = 7.3 Hz, 3 H, CH_2CH_3), 0.66 (d, *J* = 7.0 Hz, 3 H, $CHCH_3$) ppm. ^{13}C NMR (75 MHz, C_6D_6): δ = 182.4, 177.4, 176.1, 143.3, 114.3, 81.3, 73.0, 71.5, 41.6, 41.1, 40.2, 40.1, 39.7, 38.2, 36.8, 36.1, 34.1, 30.3, 27.5, 26.8, 18.9, 17.4, 17.0, 14.1, 14.0 ppm. IR (neat): $\tilde{\nu}$ = 2924, 2854, 1714, 1460, 1174, 1083, 903, 770 cm^{-1}. HRMS (ESI): calcd. for $C_{25}H_{42}NaO_7$ $[M + Na]^+$ 477.2828; found 477.2834.

Methyl Ester of Amphidinin B (23): To a stirred solution of amphidinin B (**2**; 1.2 g, 2.64 mmol) in diethyl ether (20 mL) at 0 °C under a nitrogen atmosphere, was added CH_2N_2 generated by the treatment of *N*-nitroso *N*-methyl urea (1.6 g, 15.86 mmol) with 40% NaOH solution (15 mL). The reaction was stirred at 0 °C for 30 min and the organic layer was washed with a saturated solution of $NaHCO_3$ (20 mL), brine (20 mL), dried with anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude compound was purified by flash column chromatography (ethyl acetate/hexane, 1.2:8.8) to afford methyl ester **23** (1.19 g, 94%) as a colorless liquid. $[\alpha]_D^{25}$ = +6.2 (*c* = 1.2, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 5.06–4.96 (m, 1 H, RCOOCHR), 4.80 (d, *J* = 2.2 Hz, 2 H, C=CH_2), 4.50–4.40 (m, 1 H, OCHCH_2), 3.90–3.81 (m, 1 H, OCHCH_3), 3.68 (s, 3 H, $COOCH_3$), 3.65 (s, 3 H, $COOCH_3$), 2.72–2.57 (m, 1 H, OCOCHCH_3), 2.47–2.09 (m, 6 H, CH_2COOCH_3, CH_2C=CH_2, $CH(CH_3)COOCH_3$ and CH_2C=CH_2), 1.89–1.24 (m, 16 H, CH_2C=CH_2, OCHCH_2CH_3, $CHCH_3$ and $(CH_2)_6$), 1.15 (d, *J* = 6.8 Hz, 3 H, $CHCH_3$), 1.11 (d, *J* = 6.7 Hz, 3 H, $CHCH_3$), 0.94–0.88 (m, 6 H, $CHCH_3$ and CH_2CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.6, 176.4, 171.7, 142.7, 114.3, 81.3, 72.9, 71.3, 51.5, 51.4, 41.4, 40.7, 40.0, 39.7, 37.9, 36.2, 35.7, 33.7, 30.1, 29.7, 27.4, 26.4, 18.6, 17.1, 17.0, 13.9, 13.8 ppm. IR (neat): $\tilde{\nu}$ = 2934, 2864, 1735, 1458, 1376, 1252, 1168, 1088, 1008, 901, 757 cm^{-1}. HRMS (ESI): calcd. for $C_{27}H_{46}NaO_7$ $[M + Na]^+$ 505.3141; found 505.3134.

Supporting Information (see also the footnote on the first page of this article): ^1H and ^{13}C NMR spectra for all compounds are available.

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