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Total synthesis of a novel macrotetrolide

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ABSTRACT

The total synthesis of a novel macrotetrolide, an isobutyl nonactin analog, has been achieved in 15% yield by coupling both enantiomers of the corresponding nonactic acid analogs followed by macrolactonization. These building blocks were prepared starting from β-ketoester in nine steps and 34% overall yield, in an efficient and highly stereoselective sequence. The key steps of the strategy are asymmetric hydrogenation, chelation-controlled allylation, intramolecular haloetherification of bishomoallylic ether presenting a trisubstituted double bond deactivated by an ester, and finally a stereoselective reduction of α-bromoester.

1. Introduction

Macrotetrolides, and in particular nactins (Fig. 1), display a wide range of biological activities,[1] such as antimicrobial, insecticidal, antifungal, and immunosuppressive. The total synthesis of nonactin **1**, the lowest homolog of the nactin family, has been achieved by six groups[2] and to our knowledge, only one synthesis of a non-natural nonactin analog (macrotetrolide α) has been reported.[3]

These macrolactones are composed of both enantiomers of nonactic, homononactic or bishomononactic acids. It has been shown that the bigger the alkyl groups size (R_1–R_4), the better the antimicrobial and antifungal activities.[1] The latter are correlated to the ability of such a compound to complex cations. It is the reason why nonactin is also used for the preparation of ion selective electrodes.[4]

Herein, we report an efficient and highly stereoselective synthesis of a novel synthetic nonactin analog. A general retrosynthetic analysis is presented in Scheme 1.

Coupling of (+) and (−)-nonactic acid analogs **A**, followed by macrolactonization, would lead to the macrotetrolide. The (+) and (−)-nonactic acid analogs **A** could be prepared using the same strategy; only the formation of (−)-**A** is depicted in Scheme 1. We envisaged its synthesis from α-bromo-THF **B** via a radical-mediated reduction. The *cis*-THF **B** could be built from the bishomoallylic ether **C** using a diastereoselective haloetherification. This ether **C** could be synthesized via a double bond homologation sequence from homoallylic alcohol **D**. The latter could be obtained by a stereoselective allylation of the aldehyde **E**, easily accessible from β-ketoester **F**.

2. Results and discussion

2.1. Synthesis of nonactic acid analogs

Our synthesis (Scheme 2) started with the catalytic asymmetric reduction of 5-methyl-3-oxo-hexanoic acid ethyl ester **10**. Hydrogenation[5] of **10** with $RuCl_2$[(*R*)-BINAP] afforded (3*R*)-3-hydroxyester **11** in 96% yield and 97% ee.[6] Protection of the secondary alcohol **11** with benzyl-2,2,2-trichloroacetimidate in the presence of triflic acid[7] yielded the β-benzyloxyester **12** (85%), which was then reduced to aldehyde **13** (90%) with DIBAL-H at −78 °C in ether.[8] The introduction of the second

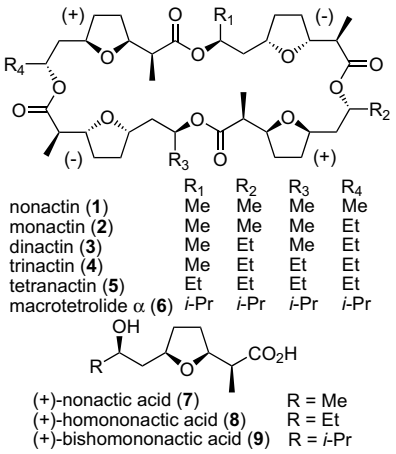

Figure 1. Structures of naturally occurring macrotetrolides, macrotetrolide α and the monomer precursor acids.

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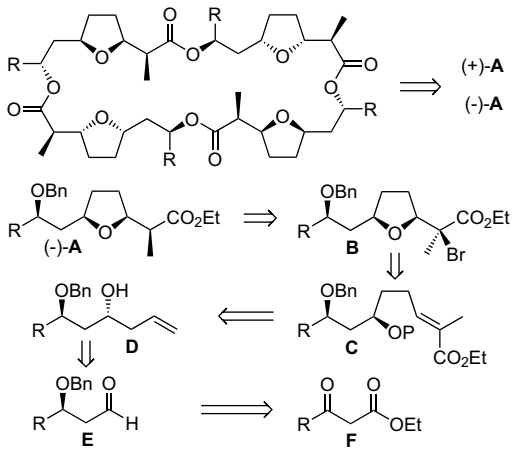


Scheme 1. Synthetic plan.

stereocenter was achieved via 1,3-asymmetric induction. Chelation-controlled allylation[9] of β-benzyloxyaldehyde **13**, promoted by $TiCl_4$, led to product **14** with excellent yield and diastereoselectivity (*anti*:*syn*=98:2, determined by GC analysis of the crude mixture and after purification). Alcohol **14** (96% dr) was therefore converted to its 2,6-dichlorobenzylether (DCB) **15** (97%, detected as a single isomer by NMR spectroscopy after purification), since Rychnovsky and Bartlett[10] and more recently White et al.[11] observed a highly stereoselective haloetherification with this protecting group for the synthesis of *cis*-2,5-disubstituted tetrahydrofuran. The terminal alkene **15** was transformed into primary alcohol **16** (90%) via a highly regioselective sequence of hydroboration/oxidation with 9-BBN/H_2O_2/NaOAc.[12] The Swern oxidation of this primary alcohol **16** was followed by in situ Wittig reaction[13] to give a 97:3 (*E*:*Z*) mixture of isomeric products from which the major (*E*)-bishomoallylic ether **17** was isolated in 69% yield after column chromatography.

Our first attempts at electrophilic cyclization of compound **17** with iodine in acetonitrile, according to Bartlett,[10] were unsuccessful. However, with iodine monobromide or bromine, the formation of α-halo-*cis*-THF occurred. The best results were obtained with bromine. Bromo-*cis*-THF **18** was obtained in 90% yield and as a single diastereoisomer (determined by ^{1}H NMR spectroscopy).

Finally, a radical-mediated reduction of α-bromo-THF **18** using $(Me_3Si)_3SiH$ and AIBN, at −25 °C in toluene and under UV irradiation, gave the desired protected nonactic acid analog **19** in 85% yield. Analysis of the crude reaction mixture by ^{1}H NMR spectroscopy indicated that the diastereoisomeric excess (86%) was in favor of the 1,2-*anti* product.[14] These results are consistent with Guindon's ones.[15]

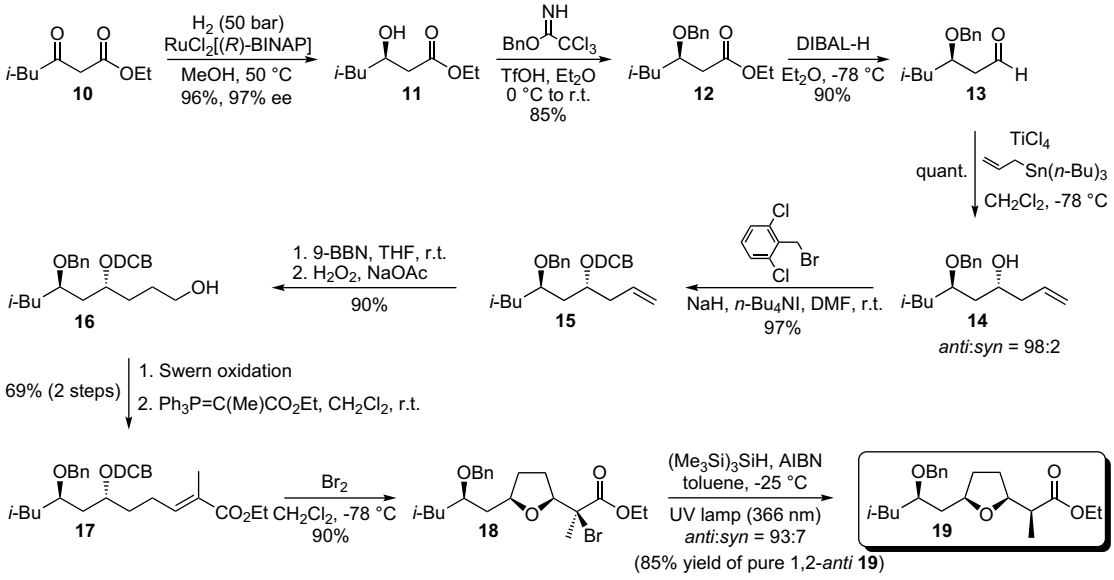
The synthesis of the (+)-**19** enantiomer was performed in the same way, starting from the β-ketoester **10**, which was hydrogenated in methanol at 50 °C under 50 bar in the presence of $RuCl_2$[(*S*)-BINAP]. The overall yield was similar to that obtained for the synthesis of compound (−)-**19**.

2.2. Determination of the absolute and relative configurations

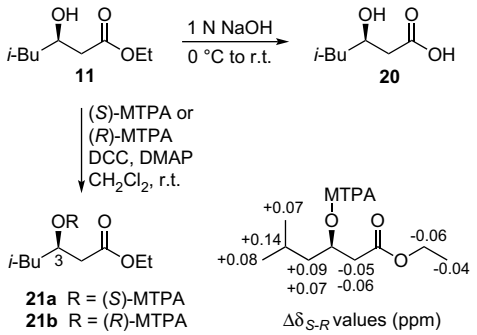
Alcohol (*R*)-**11** has already been formed by asymmetric reduction of β-ketoester **10** with *Saccharomyces cerevisiae* and has been reported to present an optical rotation of +10.3 (*c* 8.0, $CHCl_3$).[6a] By asymmetric hydrogenation of **10** in the presence of $RuCl_2$[(*R*)-BINAP] catalyst, we measured for alcohol **11** an optical rotation of −12.9 (*c* 8.0, $CHCl_3$). According to the quadrant rule,[16] we expected the formation of the (*R*)-enantiomer. In order to confirm this hypothesis, a chemical transformation of the ethyl ester **11** to acid **20** was performed (Scheme 3). The optical rotation for compound **20** ($[\alpha]_D^{20}$=−13.9 (*c* 1.05, $CHCl_3$)) was consistent with the (*R*)-enantiomer; the value for the (*S*)-**20** enantiomer (99% ee) being +14.2 (*c* 1.2, $CHCl_3$).[17]

The absolute configuration of **11** was also determined by application of the modified Mosher's method.[18] Alcohol **11** was treated with (*S*)- and (*R*)-2-methoxy-2-phenyl-2-(trifluoromethyl)acetic acid (MTPA) to give, respectively, the (*S*)- and (*R*)-MTPA derivatives (**21a** and **21b**). The calculation of the $\Delta\delta_{S-R}$ values clearly established the absolute configuration of C-3 as *R* (Scheme 3).

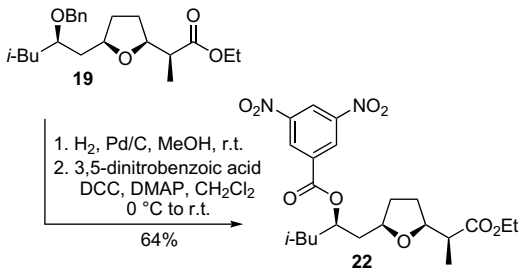
Relative configurations of the stereocenters were confirmed by crystallographic analysis of the dinitrobenzoate derivative **22**, obtained from compound **19** via subsequent debenzylation and esterification with 3,5-dinitrobenzoic acid (Scheme 4 and Fig. 2).



Scheme 2. Synthesis of nonactic acid analog.



Scheme 3. Determination of the absolute configuration.



Scheme 4. Determination of the relative configurations.

2.3. Synthesis of the macrotetrolide

We applied (−)-**19** and (+)-**19** in the synthesis of the corresponding nonactin analog. For that, it was necessary to deprotect selectively a terminal carbonyl function in the presence of a non-terminal one. It is the reason why the ethyl ester (−)-**19** was transformed into its corresponding 2-trimethylsilylethyl ester **25** (TMSE) (Scheme 5), which gave easily the acid in the presence of tetrabutylammonium fluoride (TBAF).[19] Thus, saponification with KOH in MeOH/H_2O,[14] esterification with 2-trimethylsilylethanol in the presence of diisopropylcarbodiimide (DIC) and DMAP[20] followed by hydrogenolysis of the benzyl ether function afforded the hydroxyester **25** in 60% yield (three steps) (Scheme 5). As for the ester (+)-**19**, it was hydrolyzed with KOH in MeOH/H_2O to yield the corresponding acid (+)-**23**, which was then submitted to esterification with the hydroxyester **25** in the presence of DCC and DMAP. The resulting dimer **26**, formed in 73% yield, was then divided into two parts. The first aliquot was treated with TBAF in order to generate the acid function (compound **27**) and the second one with hydrogen to lead to the free hydroxyl group (compound **28**). For the preparation of the linear tetramer, esterification between compounds **27** and **28** was performed under Yamaguchi et al. conditions.[21] After desilylation, hydrogenolysis, subsequent intramolecular modified Yamaguchi procedure[22] furnished the isobutyl analog of nonactin **32**. The latter was obtained in 15% overall yield starting from (+) and (−)-**19**.

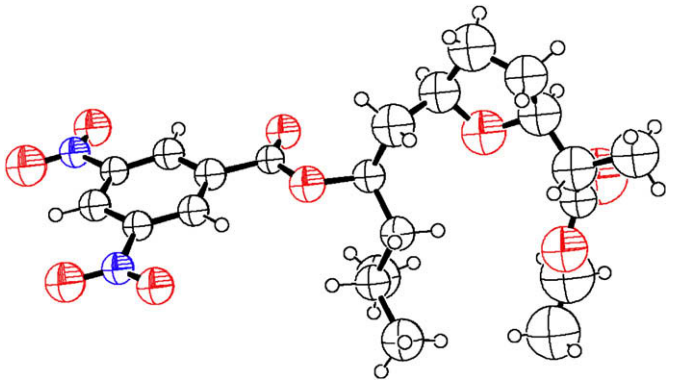


Figure 2. ORTEP drawing of **22**.

3. Conclusion

We have reported a total stereoselective synthesis of protected nonactic acid analog **19** from β-ketoester **10**, in nine steps and 34% overall yield. The key steps of this synthesis sequence were the asymmetric hydrogenation, the allylation reaction, a *cis*-cyclo bromoetherification followed by a radical-mediated dehalogenation; all the reactions being highly stereocontrolled.

The two protected enantiomers (+)-**19** and (−)-**19**, analogs of nonactic acid, were submitted to esterification then macrolactonization in order to produce the isobutyl analog of nonactin **32** in 15% overall yield.

4. Experimental

4.1. General

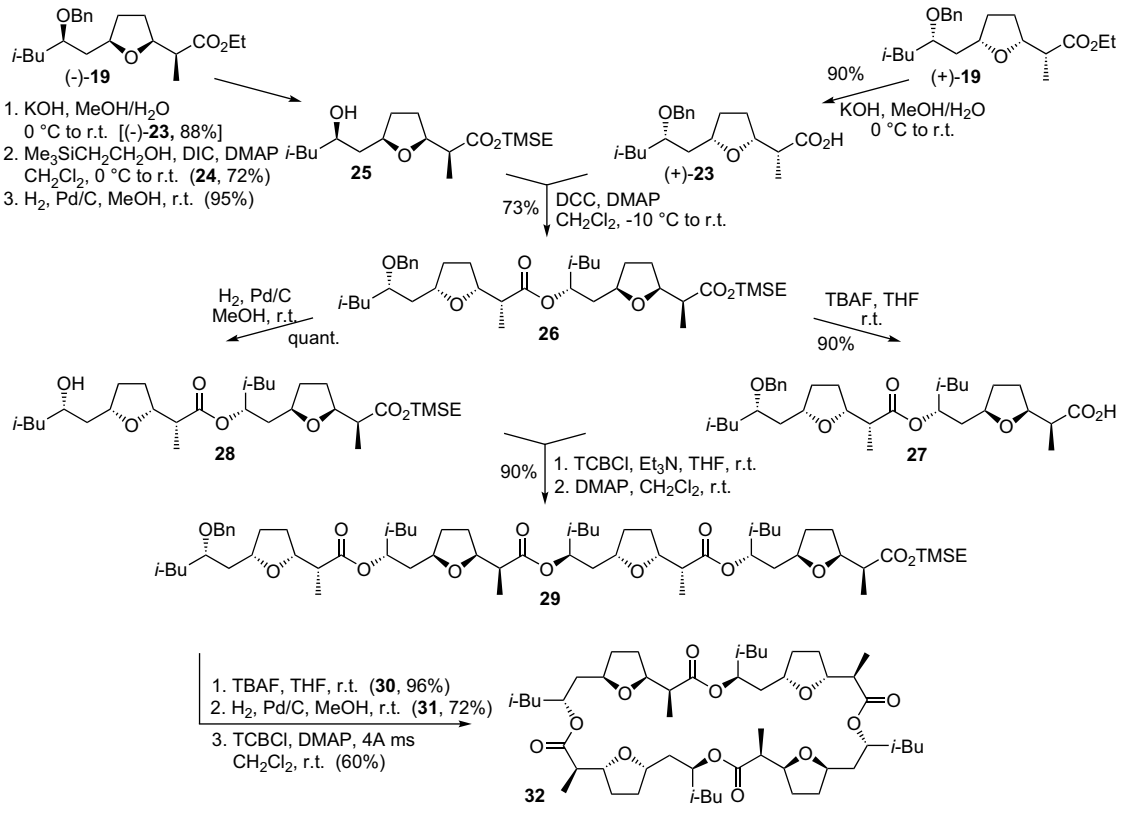
All commercial materials were used without further purification unless otherwise noted. Et_2O and THF were distilled over sodium benzophenone ketyl. Dichloromethane, toluene, DMF, and DMSO were distilled from calcium hydride. All reactions were performed under a dry argon atmosphere in oven-dried glassware. Flash chromatography was performed on Merck silica gel (40–63 μm). Analytical thin-layer chromatography was carried out on Merck silica gel $60F_{254}$. Optical rotations were measured with a Perkin Elmer 343 polarimeter at the sodium D line with a 1-dm path length, 1-mL cell. NMR spectra were recorded on a Bruker AC400 and are referenced to TMS as internal standard. IR spectra were recorded on a Nicolet Avatar 370 DTGS infrared spectrometer. Elemental analyses were performed by the Service de Microanalyse de l'Institut de Chimie des Substances Naturelles, Gif-sur-Yvette. High-resolution mass spectra were recorded on a Waters Micromass® GCT Premier™. Chiral GC was performed on an HP 6890 with He as carrier gas and using an Rt-βDEX cst™ column (30 m, 0.5 mm id, 0.25 μm df). Radical-mediated reactions were carried out using a Hamamatsu UV Spot Light Source (200W type L8222-01).

4.2. Ethyl 3-hydroxy-5-methylhexanoate (11)

(*R*)-BINAP (53 mg, 0.084 mmol) and $[(benzene)RuCl_2]_2$ (20 mg, 0.04 mmol) were dissolved in degassed DMF (1.4 mL) under argon. The reaction was heated to 100 °C for 10 min. After cooling to 50 °C, the solvent was removed under vacuum to give the catalyst as an orange-red solid. This catalyst (5 mg) was dissolved in a degassed solution of β-ketoester **10** (1.72 g, 10.0 mmol) in MeOH (1.5 mL). The mixture was transferred to an autoclave, which was purged three times with hydrogen. The mixture was stirred overnight at 50 °C under a pressure of 50 bar. After carefully venting the hydrogen at room temperature, the solvent was removed and the residue dissolved in Et_2O. The ether solution was filtered through a pad of silica gel. Evaporation of the solvent gave the pure β-hydroxyester **11** as a colorless oil (1.67 g, 96%). (3*R*)-**11**: $[\alpha]_D^{20}=-12.9$ (*c* 8.0, $CHCl_3$). With (*S*)-BINAP, (3*S*)-**11** was obtained: $[\alpha]_D^{20}=+13.3$ (*c* 8.0, $CHCl_3$).

4.3. Ethyl 3-(benzyloxy)-5-methylhexanoate (12)

To a stirred solution of β-hydroxyester **11** (870 mg, 5.00 mmol) and benzyl-2,2,2-trichloroacetimidate (2.53 g, 10.0 mmol) in Et_2O



Scheme 5. Synthesis of the macrotetrolide.

(10 mL) was added, at room temperature, trifluoromethanesulfonic acid (44 μL, 0.50 mmol). The mixture was stirred overnight and concentrated. The residue was taken up with cyclohexane and the crystalline trichloroacetamide removed by filtration. The filtrate was washed with brine, dried ($MgSO_4$), and concentrated. The crude mixture was purified by flash chromatography (cyclohexane/AcOEt, 95/5) to give the β-benzyloxyester **12** as a colorless oil (1.12 g, 85%). (3*R*)-**12**: $[\alpha]_D^{20}=+10.0$ (*c* 1.0, $CHCl_3$); (3*S*)-**12**: $[\alpha]_D^{20}=-8.9$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 3H, *J*=6.6 Hz), 0.91 (d, 3H, *J*=6.6 Hz), 1.25 (t, 3H, *J*=7.2 Hz), 1.29 (ddd, 1H, *J*=13.9, 8.1, 5.0 Hz), 1.60 (ddd, 1H, *J*=13.9, 8.0, 5.8 Hz), 1.7–1.9 (m, 1H), 2.46 (dd, 1H, *J*=15.0, 5.7 Hz), 2.62 (dd, 1H, *J*=15.0, 6.8 Hz), 3.9–4.0 (m, 1H), 4.14 (q, 1H, *J*=7.2 Hz), 4.15 (q, 1H, *J*=7.2 Hz), 4.51 (d, 1H, *J*=11.3 Hz), 4.58 (d, 1H, *J*=11.3 Hz), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.2, 23.1, 24.5, 40.2, 44.1, 60.3, 71.4, 74.4, 127.5, 127.7, 128.2, 138.4, 171.7; IR (film) 3089, 3065, 3031, 2956, 2870, 1950, 1877, 1736, 1603, 1496, 1466, 1454, 1368, 1307, 1240, 1179, 1096, 1069, 1029, 735, 697. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.73; H, 9.27.

4.4. 3-(Benzyloxy)-5-methylhexanal (13)

To a stirred solution of β-benzyloxyester **12** (793 mg, 3.00 mmol) in Et_2O (6 mL) was added dropwise, at −78 °C, a 1 M solution of DIBAL in toluene (4.2 mL, 4.2 mmol), and stirring was continued at −78 °C for at least 1 h. Upon complete consumption of ester, the reaction mixture was quenched with a 2 N hydrochloric acid solution (12 mL) and the temperature allowed to warm up to room temperature. The aqueous phase was separated and extracted twice with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (cyclohexane/AcOEt, 9/1) to give the β-benzyloxyaldehyde **13** as a colorless oil (596 mg, 90%). (3*R*)-**13**: $[\alpha]_D^{20}=+4.10$ (*c* 24.9, $CHCl_3$); (3*S*)-**13**: $[\alpha]_D^{20}=-1.8$ (*c* 10.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, 3H, *J*=6.5 Hz), 0.92 (d, 3H, *J*=6.5 Hz), 1.32 (ddd, 1H, *J*=13.8, 7.6, 5.7 Hz), 1.66 (ddd, 1H, *J*=13.8, 7.5, 6.3 Hz), 1.7–1.8 (m, 1H), 2.59 (ddd, 1H, *J*=16.2, 5.1, 2.0 Hz), 2.67 (ddd, 1H, *J*=16.2, 6.5, 2.6 Hz), 3.9–4.1 (m, 1H), 4.53 (d, 1H, *J*=11.3 Hz), 4.54 (d, 1H, *J*=11.3 Hz), 7.2–7.4 (m, 5H), 9.82 (dd, 1H, *J*=2.6, 2.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.3, 22.8, 24.4, 43.8, 48.4, 71.0, 72.6, 127.5, 127.6, 128.2, 138.0, 201.4; IR (film) 3089, 3064, 3031, 2956, 2928, 2870, 2726, 1951, 1875, 1724, 1604, 1497, 1467, 1454, 1386, 1367, 1354, 1308, 1244, 1207, 1171, 1142, 1096, 1069, 1028, 737, 698. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.38; H, 9.05.

4.5. 6-(Benzyloxy)-8-methylnon-1-en-4-ol (14)

To a stirred solution of β-benzyloxyaldehyde **13** (980 mg, 4.45 mmol) in CH_2Cl_2 (45 mL) was added, at −78 °C, $TiCl_4$ (freshly distilled over copper, 488 μL, 4.45 mmol). After 2 min, allyltributyltin (1.65 mL, 5.34 mmol) was added dropwise and stirring was continued at −78 °C for at least 30 min. Upon complete consumption of aldehyde, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and the temperature allowed to warm up to room temperature. The aqueous phase was separated and extracted twice with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane/AcOEt, 95/5) to give the alcohol **14** as a colorless oil (1.17 g, quantitative yield, 96% dr). (4*R*,6*R*)-**14**: $[\alpha]_D^{20}=-25.6$ (*c* 2.0, $CHCl_3$); (4*S*,6*S*)-**14**: $[\alpha]_D^{20}=+24.0$ (*c* 2.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 6H, *J*=6.3 Hz), 1.2–1.4 (m, 1H), 1.58 (ddd, 1H, *J*=14.7, 6.5, 2.4 Hz), 1.6–1.8 (m, 2H), 1.76 (ddd, 1H, *J*=14.7, 9.6, 3.5 Hz), 2.2–2.3 (m, 2H), 2.88 (d, *J*=3.0 Hz), 3.78 (m, 1H), 3.9–4.1 (m, 1H), 4.56 (s, 2H), 5.09 (dm, 1H, *J*=10.5 Hz), 5.10 (dm, 1H, *J*=16.8 Hz), 5.83 (ddt, 1H, *J*=16.8, 10.5, 7.1 Hz), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.8, 22.9, 24.7, 39.4, 42.2, 42.9, 67.7, 71.1, 75.5, 117.4, 127.7, 127.9 (2C), 128.4 (2C), 134.9, 138.3; IR (film) 3443, 3067, 3031, 2955, 2928, 2869, 1948, 1826,

1641, 1605, 1497, 1467, 1454, 1433, 1385, 1366, 1308, 1246, 1207, 1170, 1147, 1090, 1068, 1028, 997, 914, 868, 845, 816, 735, 697. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.77; H, 9.94.

4.6. 6-(Benzyloxy)-4-(2,6-dichlorobenzyloxy)-8-methylnon-1-ene (15)

To a suspension of NaH (60% dispersion in mineral oil, 64 mg, 1.60 mmol) in DMF (6.5 mL) was added, at 0 °C, a solution of alcohol **14** (210 mg, 0.80 mmol) in DMF (0.7 mL). The mixture was stirred for 20 min at 0 °C, and a solution of 2,6-dichlorobenzyl bromide (395 mg, 1.60 mmol) in DMF (1.3 mL) was added slowly, followed by Bu_4NI (59 mg, 0.16 mmol) at 0 °C. The resulting mixture was stirred overnight at room temperature, then quenched with saturated aqueous NH_4Cl solution, and diluted with Et_2O. The aqueous phase was separated and the organic layer was washed with H_2O and brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane/AcOEt, 95/5) to give the product **15** as a colorless oil (328 mg, 97%). (4*R*,6*R*)-**15**: $[\alpha]_D^{20}=-54.4$ (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J*=6.5 Hz), 0.89 (d, 3H, *J*=6.5 Hz), 1.26 (ddd, 1H, *J*=13.6, 6.8, 6.8 Hz), 1.53 (ddd, 1H, *J*=13.6, 6.7, 6.7 Hz), 1.6–1.7 (m, 2H), 1.6–1.8 (m, 1H), 2.4–2.5 (m, 2H), 3.69 (m, 1H), 3.7–3.8 (m, 1H), 4.23 (d, 1H, *J*=11.3 Hz), 4.46 (d, 1H, *J*=11.3 Hz), 4.73 (d, 1H, *J*=10.5 Hz), 4.84 (d, 1H, *J*=10.5 Hz), 5.08 (dm, 1H, *J*=10.1 Hz), 5.11 (dm, 1H, *J*=17.1 Hz), 5.88 (ddt, 1H, *J*=17.1, 10.1, 7.1 Hz), 7.12 (dd, 1H, *J*=8.5, 7.6 Hz), 7.2–7.4 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.1, 24.6, 38.3, 40.5, 43.9, 65.1, 70.8, 74.7, 75.1, 117.3, 127.3, 127.5 (2C), 128.2–128.3 (4C), 129.8, 133.8, 134.4, 136.8 (2C), 139.1; IR (film) 3067, 3030, 2954, 2868, 1945, 1864, 1722, 1640, 1582, 1564, 1496, 1467, 1454, 1437, 1385, 1365, 1306, 1247, 1198, 1147, 1094, 1065, 1028, 994, 914, 853, 826, 778, 767, 733, 697; HRMS (Cl^+, methane) *m/z* $[M+H]^+$ Calcd for $C_{24}H_{31}Cl_2O_2$: 421.1701, found: 421.1696.

4.7. 6-(Benzyloxy)-4-(2,6-dichlorobenzyloxy)-8-methylnonan-1-ol (16)

To a stirred solution of **15** (1.85 g, 4.41 mmol) in THF (20 mL) was added dropwise, at 0 °C, a 0.5 M solution of 9-BBN in THF (26.4 mL, 13.2 mmol). The mixture was stirred at 0 °C for 1 h and at room temperature overnight. The reaction mixture was cooled to 0 °C, EtOH (3.9 mL), saturated aqueous NaOAc (13.4 mL), and 30% H_2O_2 (4.3 mL) were added in that order; stirring was continued at 0 °C for 1 h and at room temperature for 5 h. The mixture was diluted with Et_2O (150 mL), washed twice with H_2O, saturated aqueous $NaHCO_3$ solution, saturated aqueous NH_4Cl solution, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane/AcOEt, 8/2) to give the alcohol **16** as a colorless oil (1.76 g, 90%). (4*R*,6*R*)-**16**: $[\alpha]_D^{20}=-47.2$ (*c* 1.0, $CHCl_3$); (4*S*,6*S*)-**16**: $[\alpha]_D^{20}=+40.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H, *J*=6.6 Hz), 0.90 (d, 3H, *J*=6.6 Hz), 1.27 (ddd, 1H, *J*=13.7, 6.7, 6.7 Hz), 1.5–1.8 (m, 9H), 3.6–3.7 (m, 3H), 3.7–3.8 (m, 1H), 4.26 (d, 1H, *J*=11.3 Hz), 4.49 (d, 1H, *J*=11.3 Hz), 4.73 (d, 1H, *J*=10.4 Hz), 4.79 (d, 1H, *J*=10.4 Hz), 7.14 (dd, 1H, *J*=8.5, 7.6 Hz), 7.2–7.4 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9, 23.1, 24.6, 27.9, 30.2, 40.3, 43.8, 63.0, 65.1, 70.8, 74.9, 75.6, 127.3, 127.6 (2C), 128.2–128.4 (4C), 129.8, 133.7, 136.8 (2C), 138.9; IR (film) 3404, 3088, 3064, 3030, 2951, 2924, 2868, 1946, 1865, 1806, 1582, 1564, 1496, 1468, 1454, 1436, 1385, 1365, 1247, 1197, 1171, 1146, 1094, 1059, 993, 854, 826, 778, 767, 733, 697. Anal. Calcd for $C_{24}H_{32}Cl_2O_3$: C, 65.60; H, 7.34. Found: C, 65.54; H, 7.31.

4.8. Ethyl 8-(benzyloxy)-6-(2,6-dichlorobenzyloxy)-2,10-dimethylundec-2-enoate (17)

To a stirred solution of oxalyl chloride (1.51 mL, 17.6 mmol) in CH_2Cl_2 (120 mL) was added dropwise, at −78 °C, DMSO (1.59 mL, 22.4 mmol), and the resulting mixture was stirred for 30 min. Subsequently, a solution of alcohol **16** (3.52 g, 8.00 mmol) in CH_2Cl_2 (30 mL) was added over 5 min giving a white precipitate. After stirring at −78 °C for 10 min, Et_3N (5.40 mL, 38.9 mmol) was added. After 15 min, the reaction mixture was allowed to warm up to 0 °C and stirred for 1 h. Then, (carbethoxyethylidene)-triphenylphosphorane (4.35 g, 12.0 mmol) was added at 0 °C, and the resultant mixture stirred at room temperature overnight. The reaction mixture was diluted with Et_2O (80 mL), washed twice with H_2O, brine, then dried ($MgSO_4$), and concentrated. The residue was taken up with cyclohexane, filtered, and concentrated. Purification by flash chromatography (cyclohexane/AcOEt, 95/5) gave the pure (*E*)-bishomoallylic ether **17** as a colorless oil (2.86 g, 69%). (2*E*,6*R*,8*R*)-**17**: $[\alpha]_D^{20}=-28.9$ (*c* 1.1, $CHCl_3$); (2*E*,6*S*,8*S*)-17: $[\alpha]_D^{20}=+31.0$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H, *J*=6.6 Hz), 0.91 (d, 3H, *J*=6.6 Hz), 1.2–1.4 (m, 1H), 1.30 (t, 3H, *J*=7.1 Hz), 1.5–1.7 (m, 2H), 1.6–1.8 (m, 4H), 1.84 (s, 3H), 2.2–2.4 (m, 2H), 3.6–3.8 (m, 2H), 4.19 (q, 2H, *J*=7.1 Hz), 4.27 (d, 1H, *J*=11.3 Hz), 4.49 (d, 1H, *J*=11.3 Hz), 4.72 (d, 1H, *J*=10.4 Hz), 4.78 (d, 1H, *J*=10.4 Hz), 6.77 (tm, 1H, *J*=7.4 Hz), 7.14 (dd, 1H, *J*=8.5, 7.5 Hz), 7.2–7.4 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 14.3, 22.9, 23.1, 24.0, 24.6, 32.7, 40.4, 43.9, 60.3, 65.1, 70.8, 74.8, 75.3, 121.4, 127.3, 127.6 (2C), 128.0, 128.2–128.4 (4C), 129.8, 133.7, 136.8 (2C), 138.9, 141.8, 168.1; IR (film) 3088, 3064, 3030, 2954, 2928, 2869, 1947, 1865, 1712, 1650, 1582, 1564, 1496, 1466, 1454, 1437, 1386, 1366, 1273, 1261, 1196, 1135, 1094, 1075, 1029, 993, 918, 855, 826, 779, 767, 736, 697. Anal. Calcd for $C_{29}H_{38}Cl_2O_4$: C, 66.79; H, 7.34. Found: C, 66.77; H, 7.25.

4.9. Ethyl 2-{5-[2-(benzyloxy)-4-methylpentyl]tetrahydrofuran-2-yl}-2-bromopropanoate (18)

To a stirred solution of bishomoallylic ether **17** (2.86 g, 5.49 mmol) in CH_2Cl_2 (275 mL) was added slowly, at −78 °C, a 1.0 M solution of Br_2 in CH_2Cl_2 (freshly prepared, 7.70 mL, 7.70 mmol). The resulting brown solution was stirred in the dark at −78 °C. After complete consumption of starting material (≈1 h), the reaction mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution and diluted with Et_2O. The aqueous phase was separated and extracted twice with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane/AcOEt, 95/5) to give the α-bromotetrahydrofuran **18** as a colorless oil (2.18 g, 90%). (2*S*,3*S*,6*R*,8*R*)-**18**: $[\alpha]_D^{20}=-26.4$ (*c* 1.0, $CHCl_3$); (2*R*,3*R*,6*S*,8*S*)-**18**: $[\alpha]_D^{20}=+25.3$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 6H, *J*=6.6 Hz), 1.26 (ddd, 1H, *J*=13.6, 7.3, 6.2 Hz), 1.29 (t, 3H, *J*=7.1 Hz), 1.4–1.6 (m, 2H), 1.6–1.8 (m, 3H), 1.84 (s, 3H), 1.9–2.1 (m, 2H), 2.0–2.2 (m, 1H), 3.5–3.7 (m, 1H), 4.11 (m, 1H), 4.24 (q, 2H, *J*=7.1 Hz), 4.42 (dd, 1H, *J*=8.0, 5.6 Hz), 4.51 (s, 2H), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.6, 22.7, 22.8, 24.5, 28.3, 31.9, 41.0, 44.2, 61.8, 61.9, 71.3, 75.1, 78.0, 81.9, 127.3, 127.7 (2C), 128.1 (2C), 138.8, 170.3; IR (film) 3088, 3064, 3030, 2955, 2869, 1949, 1875, 1739, 1604, 1460, 1366, 1263, 1213, 1173, 1070, 963, 910, 862, 806, 735, 698. Anal. Calcd for $C_{22}H_{33}BrO_4$: C, 59.86; H, 7.54. Found: C, 59.88; H, 7.52.

4.10. Ethyl 2-{5-[2-(benzyloxy)-4-methylpentyl]-tetrahydrofuran-2-yl}propanoate (19)

To a stirred and degassed solution of α-bromotetrahydrofuran **18** (221 mg, 0.50 mmol) and AIBN (12 mg, 0.08 mmol) in dry toluene (5 mL) was added dropwise, at −25 °C, $(Me_3Si)_3SiH$ (233 μL, 0.75 mmol). The reaction mixture was irradiated for 1.5 h with an UV lamp (366 nm) and then concentrated. The residue was taken up with cyclohexane (5 mL) and treated with a 1 M solution of TBAF in THF (1.25 mL, 1.25 mmol) for 5 min at room temperature. After filtration of the mixture through

a short pad of silica gel and solvent removal, a residue was obtained and subsequently purified by flash chromatography (cyclohexane/AcOEt, 9/1) to yield, as a colorless oil, the major isomer **19** (153 mg, 85%). (2*S*,3*S*,6*R*,8*R*)-**19**: $[\alpha]_D^{20}=-9.30$ (*c* 1.0, $CHCl_3$); (2*R*,3*R*,6*S*,8*S*)-**19**: $[\alpha]_D^{20}=+10.5$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J*=6.5 Hz), 0.90 (d, 3H, *J*=6.5 Hz), 1.11 (d, 3H, *J*=7.0 Hz), 1.26 (t, 3H, *J*=7.1 Hz), 1.27 (ddd, 1H, *J*=13.6, 7.5, 5.9 Hz), 1.4–1.8 (m, 6H), 1.9–2.1 (m, 2H), 2.50 (dq, 1H, *J*=8.2, 7.0 Hz), 3.5–3.7 (m, 1H), 4.0–4.1 (m, 2H), 4.15 (q, 1H, *J*=7.1 Hz), 4.15 (q, 1H, *J*=7.1 Hz), 4.51 (d, 1H, *J*=11.3 Hz), 4.53 (d, 1H, *J*=11.3 Hz), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.2, 22.7, 23.0, 24.6, 28.6, 31.5, 41.8, 44.5, 45.6, 60.2, 71.6, 75.4, 76.5, 80.3, 127.3, 127.8 (2C), 128.2 (2C), 139.0, 174.9; IR (film) 3088, 3064, 3030, 2954, 2870, 1948, 1876, 1732, 1604, 1497, 1455, 1368, 1332, 1300, 1259, 1188, 1157, 1067, 1029, 952, 905, 862, 806, 736, 698. Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 72.68; H, 9.43.

4.11. (3*R*)-3-Hydroxy-5-methylhexanoic acid (20)

A solution of ester **11** (105 mg, 0.60 mmol) in 1 N NaOH (3 mL) was stirred at 0 °C, then allowed to warm up to room temperature and stirred overnight. The reaction mixture was washed with ether, the aqueous layer was acidified with dilute HCl to pH≈1, and then extracted twice with AcOEt. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give the acid **20** as a white solid (77 mg, 88%). (3*R*)-**20**: $[\alpha]_D^{20}=-13.9$ (*c* 1.05, $CHCl_3$).

4.12. Preparation of the (*S*)- and (*R*)-MTPA esters (21a and 21b)

To a stirred solution of alcohol **11** (44 mg, 0.25 mmol) and DMAP (7 mg, 0.06 mmol) in CH_2Cl_2 (2.5 mL) were added slowly, at 0 °C, (*S*)-MTPA (70 mg, 0.30 mmol) and DDC (62 mg, 0.30 mmol). The mixture was allowed to warm up to room temperature and stirred overnight, then concentrated. The residue was taken up with Et_2O, filtered, and concentrated. Flash chromatography (cyclohexane/AcOEt, 9/1) afforded the (*S*)-MTPA ester derivative **21a** as a colorless oil (62 mg, 63%). Through a similar procedure, the (*R*)-MTPA ester derivative **21b** was obtained as a colorless oil (59 mg, 60%) from **11** (44 mg, 0.25 mmol) using (*R*)-MTPA.

(*S*)-MTPA ester derivative (**21a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3H, *J*=6.5 Hz), 0.95 (d, 3H, *J*=6.5 Hz), 1.20 (t, 3H, *J*=7.2 Hz), 1.45 (ddd, 1H, *J*=13.5, 7.8, 5.2 Hz), 1.5–1.7 (m, 1H), 1.70 (ddd, 1H, *J*=13.5, 8.0, 5.9 Hz), 2.55 (dd, 1H, *J*=15.9, 5.3 Hz), 2.63 (dd, 1H, *J*=15.9, 7.6 Hz), 4.06 (q, 2H, *J*=7.2 Hz), 5.54 (dddd, 1H, *J*=7.8, 7.8, 5.3, 5.3 Hz).

(*R*)-MTPA ester derivative (**21b**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (d, 3H, *J*=6.5 Hz), 0.88 (d, 3H, *J*=6.5 Hz), 1.24 (t, 3H, *J*=7.2 Hz), 1.36 (ddd, 1H, *J*=13.6, 8.3, 5.0 Hz), 1.4–1.6 (m, 1H), 1.63 (ddd, 1H, *J*=13.6, 8.3, 5.4 Hz), 2.60 (dd, 1H, *J*=15.8, 5.1 Hz), 2.69 (dd, 1H, *J*=15.8, 7.6 Hz), 4.12 (q, 2H, *J*=7.2 Hz), 5.54 (dddd, 1H, *J*=8.3, 8.3, 5.1, 5.1 Hz).

4.13. Ethyl 2-(5-{2-[3,5-dinitrobenzyloxy]-4-methylpentyl}tetrahydrofuran-2-yl)propanoate (22)

A mixture of the ether **19** (110 mg, 0.30 mmol) and 10% palladium on charcoal (64 mg) in MeOH (3 mL) was stirred for 4 h at room temperature under H_2 (1 atm). The solid was filtered off and washed with AcOEt. The filtrate was evaporated under reduced pressure. To a solution of this crude alcohol (27 mg, 0.10 mmol), 3,5-dinitrobenzoic acid (25 mg, 0.12 mmol), and DMAP (24 mg, 0.20 mmol) in CH_2Cl_2 (1 mL) was added slowly, at 0 °C, a solution of DCC (23 mg, 0.11 mmol) in CH_2Cl_2 (0.5 mL). The mixture was allowed to warm up to room temperature and stirred overnight, then concentrated. The residue was taken up with Et_2O, filtered, and concentrated. Flash chromatography (cyclohexane/AcOEt, 95/5) afforded the 3,5-dinitrobenzoate ester **22** as white crystals (30 mg, 64%). Mp 48–50 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (d, 6H, *J*=6.5 Hz), 1.08 (d, 3H, *J*=7.0 Hz), 1.26 (t, 3H, *J*=7.1 Hz), 1.4–1.7 (m, 4H), 1.75 (ddd, 1H, *J*=13.7, 8.2, 5.8 Hz), 1.8–2.1 (m, 4H), 2.45 (dq, 1H, *J*=8.2, 7.0 Hz), 3.9–4.1 (m, 2H), 4.13 (q, 2H, *J*=7.1 Hz), 5.4–5.5 (m, 1H), 9.1–9.3 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.3, 14.2, 22.3, 22.9, 24.8, 28.4, 31.4, 41.0, 43.8, 45.5, 60.3, 74.3, 75.8, 80.7, 122.1, 129.4 (2C), 134.5, 148.6 (2C), 162.0, 174.7; IR (film) 3105, 2959, 2873, 1731, 1629, 1598, 1548, 1462, 1345, 1277, 1172, 1075, 921, 825, 773, 730, 722; HRMS (FI) *m*/*z* $[M]^+$ Calcd for $C_{22}H_{30}N_2O_9$: 466.1951, found: 466.1949.

Crystallographic data for **22**: $C_{22}H_{30}N_2O_9$, *M*=466.48, monoclinic, space group $C2_1$, *a*=44.604(9) Å, *b*=5.648(5) Å, *c*=9.899(2) Å, $\alpha=90°$, $\beta=93.07(2)°$, $\gamma=90°$, *V*=2490.2(16) Å^3, *T*=293(2) K, *Z*=4, *d*=1.236 g/cm^3. A single crystal was used for measurement on a Siemens AED2 four-circle diffractometer equipped with a graphite monochromatized Mo Kα_1 (λ=0.71073 Å). The crystal structure was solved by direct methods using SHELX-97 and successive refinements and difference Fourier maps using SHELXL-97 program. The location of the hydrogen atoms was performed by applying the geometrical constraints using AFIX and DFIX option in SHELXL-97 program. Crystallographic data have been deposited in the Cambridge Crystallographic Data Centre (deposition number CCDC 688312). Copies of the data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1223 336 033 or deposit@ccdc.cam.ac.uk].

4.14. 2-{5-[2-(Benzyloxy)-4-methylpentyl]tetrahydrofuran-2-yl}propanoic acid (23)

To a stirred solution of ester **19** (290 mg, 0.80 mmol) in MeOH (24 mL) was added dropwise, at 0 °C, a 1 M aqueous solution of KOH (24.0 mL, 24.0 mmol). The mixture was allowed to warm up to room temperature and stirred overnight, then cooled to 0 °C. It was diluted with Et_2O (25 mL) and brine (10 mL), then acidified with a 2 M aqueous solution of HCl to pH∼1. The aqueous phase was separated and extracted twice with Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography (cyclohexane/AcOEt, 8/2+AcOH, 1%) to give the acid **23** as a colorless oil (240 mg, 90%). (2*S*,3*S*,6*R*,8*R*)-**23**: $[\alpha]_D^{20}=-25.1$ (*c* 1.0, $CHCl_3$); (2*R*,3*R*,6*S*,8*S*)-**23**: $[\alpha]_D^{20}=+26.0$ (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 3H, *J*=6.6 Hz), 0.89 (d, 3H, *J*=6.6 Hz), 1.16 (d, 3H, *J*=7.1 Hz), 1.28 (ddd, 1H, *J*=13.6, 7.3, 6.6 Hz), 1.5–1.8 (m, 5H), 1.55 (ddd, 1H, *J*=13.6, 6.8, 6.8 Hz), 1.9–2.1 (m, 2H), 2.52 (dq, 1H, *J*=8.1, 7.1 Hz), 3.5–3.7 (m, 1H), 3.9–4.1 (m, 1H), 4.0–4.2 (m, 1H), 4.51 (d, 1H, *J*=11.4 Hz), 4.54 (d, 1H, *J*=11.4 Hz), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.1, 22.8, 22.9, 24.5, 28.8, 31.4, 41.6, 44.2, 45.2, 71.3, 75.2, 76.9, 79.9, 127.4, 127.9 (2C), 128.2 (2C), 138.8, 179.7; IR (film) 3700–2200, 3088, 3064, 3030, 2957, 1949, 1866, 1806, 1716, 1605, 1587, 1497, 1464, 1420, 1384, 1366, 1328, 1290, 1227, 1170, 1144, 1070, 1028, 951, 898, 849, 736, 698. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 71.71; H, 9.01.

4.15. (2*S*,3*S*,6*R*,8*R*)-2-(Trimethylsilyl)ethyl 2-{5-[2-(benzyloxy)-4-methylpentyl]tetrahydrofuran-2-yl}propanoate (24)

To a stirred solution of acid (−)-**23** (257 mg, 0.77 mmol), DMAP (9 mg, 0.08 mmol), and 2-(trimethylsilyl)ethanol (122 μL, 0.85 mmol) in CH_2Cl_2 (4 mL) was added dropwise, at 0 °C, DIC (132 μL, 0.85 mmol). The mixture was allowed to warm up to room temperature and stirred overnight, then concentrated. The residue

was taken up with Et_2O (7 mL), filtered, and concentrated. Flash chromatography (cyclohexane/AcOEt, 95/5) afforded the ester **24** as a colorless oil (241 mg, 72%). $[\alpha]_D^{20}=-6.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.0–0.1 (m, 9H), 0.88 (d, 3H, *J*=6.5 Hz), 0.90 (d, 3H, *J*=6.5 Hz), 0.9–1.1 (m, 2H), 1.11 (d, 3H, *J*=7.0 Hz), 1.27 (ddd, 1H, *J*=13.6, 7.5, 5.8 Hz), 1.4–1.8 (m, 5H), 1.53 (ddd, 1H, *J*=13.6, 6.8, 6.8 Hz), 1.9–2.1 (m, 2H), 2.50 (dq, 1H, *J*=8.2, 7.0 Hz), 3.6–3.7 (m, 1H), 3.9–4.1 (m, 2H), 4.1–4.2 (m, 2H), 4.50 (d, 1H, *J*=11.2 Hz), 4.54 (d, 1H, *J*=11.2 Hz), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.6 (3C), 13.3, 17.3, 22.8, 23.1, 24.6, 28.5, 31.5, 41.8, 44.5, 45.7, 62.4, 71.6, 75.4, 76.5, 80.2, 127.3, 127.8 (2C), 128.2 (2C), 139.0, 175.0; IR (film) 3089, 3064, 3030, 2954, 2869, 1945, 1865, 1735, 1606, 1497, 1455, 1384, 1365, 1332, 1250, 1163, 1068, 1029, 938, 859, 838, 735, 697. Anal. Calcd for $C_{25}H_{42}O_4Si$: C, 69.08; H, 9.74. Found: C, 68.81; H, 9.53.

4.16. (2*S*,3*S*,6*R*,8*R*)-2-(Trimethylsilyl)ethyl 2-[5-(2-hydroxy-4-methylpentyl)tetrahydrofuran-2-yl]propanoate (25)

A mixture of the ether **24** (228 mg, 0.52 mmol) and 10% palladium on charcoal (110 mg) in MeOH (6 mL) was stirred overnight at room temperature under H_2 (1 atm). The solid was filtered off and washed with AcOEt. The filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/AcOEt, 8/2) to give the alcohol **25** as a colorless oil (171 mg, 95%). $[\alpha]_D^{20}=+20.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.0–0.1 (m, 9H), 0.89 (d, 3H, *J*=6.6 Hz), 0.89 (d, 3H, *J*=6.6 Hz), 0.9–1.1 (m, 2H), 1.10 (d, 3H, *J*=7.0 Hz), 1.18 (ddd, 1H, *J*=13.6, 8.3, 4.7 Hz), 1.45 (ddd, 1H, *J*=13.6, 8.7, 5.8 Hz), 1.5–1.8 (m, 5H), 1.9–2.1 (m, 2H), 2.49 (dq, 1H, *J*=8.2, 7.0 Hz), 2.74 (br s, 1H), 3.8–4.0 (m, 1H), 3.9–4.1 (m, 1H), 4.1–4.2 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.6 (3C), 13.3, 17.2, 22.2, 23.2, 24.5, 28.6, 30.7, 41.7, 45.3, 46.3, 62.6, 66.9, 77.1, 80.9, 174.8; IR (film) 3443, 2957, 2870, 1732, 1464, 1413, 1384, 1367, 1334, 1251, 1216, 1164, 1116, 1066, 938, 858, 838, 762, 694. Anal. Calcd for $C_{18}H_{36}O_4Si$: C, 62.74; H, 10.53. Found: C, 62.44; H, 10.44.

4.17. Dimer 26

To a stirred solution of acid (+)-**23** (139 mg, 0.42 mmol), alcohol **25** (143 mg, 0.42 mmol), and DMAP (13 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) was added slowly, at −10 °C, a solution of DCC (90 mg, 0.44 mmol) in CH_2Cl_2 (0.4 mL). The mixture was allowed to warm up to room temperature and stirred overnight, then concentrated. The residue was taken up with Et_2O, filtered, and concentrated. Flash chromatography (cyclohexane/AcOEt, 9/1) afforded the dimer **26** as a colorless oil (196 mg, 72%). $[\alpha]_D^{20}=+15.3$ (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.0–0.1 (m, 9H), 0.87, 0.89, 0.90 (3d, respectively, 3H, 6H, 3H, $J_1=J_2=J_3$=6.6 Hz), 0.9–1.1 (m, 2H), 1.07, 1.09 (2d, 6H, $J_1=J_2$=7.1 Hz), 1.27 (ddd, 1H, *J*=13.5, 7.4, 5.9 Hz), 1.37 (ddd, 1H, *J*=13.5, 8.3, 4.6 Hz), 1.4–1.9 (m, 12H), 1.8–2.1 (m, 4H), 2.47 (dq, 1H, *J*=7.9, 7.1 Hz), 2.50 (dq, 1H, *J*=7.8, 7.1 Hz), 3.5–3.7 (m, 1H), 3.8–3.9 (m, 1H), 3.9–4.1 (m, 3H), 4.1–4.2 (m, 2H), 4.51 (s, 2H), 4.9–5.1 (m, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.5 (3C), 13.1 (2C), 17.3, 22.2, 22.8, 23.1 (2C), 24.5, 24.6, 28.3 (2C), 31.4, 31.6, 41.3, 41.7, 43.8, 44.4, 45.3, 45.6, 62.5, 71.1, 71.5, 75.4, 76.4, 76.7, 80.0, 80.1, 127.3, 127.8 (2C), 128.2 (2C), 139.0, 174.3, 174.9; IR (film) 3087, 3063, 3030, 2956, 2872, 1946, 1866, 1737, 1606, 1496, 1462, 1382, 1366, 1333, 1252, 1188, 1165, 1065, 943, 901, 859, 838, 738, 697. Anal. Calcd for $C_{38}H_{64}O_7Si$: C, 69.05; H, 9.76. Found: C, 69.36; H, 9.99.

4.18. Dimer 27

To a solution of the ester **26** (139 mg, 0.21 mmol) in THF (1 mL) was added, at 0 °C, a 1 M solution of TBAF in THF (630 μL, 0.63 mmol). The mixture was stirred at 0 °C for 2 h and at room temperature overnight, then diluted with Et_2O (5 mL) and brine (5 mL). The phases were separated and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (cyclohexane/AcOEt, 8/2+AcOH, 1%) to give the acid **27** as a colorless oil (106 mg, 90%). $[\alpha]_D^{20}=+9.6$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88, 0.89, 0.90, 0.90 (4d, 12H, $J_1=J_2=J_3=J_4$=6.6 Hz), 1.10, 1.12 (2d, 6H, $J_1=J_2$=7.1 Hz), 1.26 (ddd, 1H, *J*=13.6, 7.5, 5.9 Hz), 1.35 (ddd, 1H, *J*=13.8, 8.3, 4.8 Hz), 1.4–1.9 (m, 12H), 1.9–2.1 (m, 4H), 2.47 (dq, 1H, *J*=8.3, 7.1 Hz), 2.51 (dq, 1H, *J*=8.2, 7.1 Hz), 3.5–3.7 (m, 1H), 3.9–4.1 (m, 4H), 4.51 (s, 2H), 5.0–5.1 (m, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.0, 13.2, 22.1, 22.8, 23.0, 23.0, 24.5, 24.5, 28.3, 28.6, 31.2, 31.5, 41.2, 41.6, 43.6, 44.3, 44.9, 45.6, 70.8, 71.4, 75.4, 76.5, 76.9, 79.9, 80.0, 127.3, 127.7 (2C), 128.2 (2C), 138.8, 174.4, 179.1; IR (film) 3700–2200, 3089, 3064, 3030, 2953, 2870, 1949, 1873, 1732, 1714, 1497, 1463, 1456, 1418, 1384, 1367, 1260, 1192, 1169, 1142, 1068, 1029, 950, 902, 849, 736, 698. Anal. Calcd for $C_{33}H_{52}O_7$: C, 70.68; H, 9.35. Found: C, 70.66; H, 9.32.

4.19. Dimer 28

A mixture of the ether **26** (123 mg, 0.19 mmol) and 10% palladium on charcoal (40 mg) in MeOH (2 mL) was stirred overnight at room temperature under H_2 (1 atm). The solid was filtered off and washed with AcOEt. The filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/AcOEt, 7/3) to give the alcohol **28** as a colorless oil (108 mg, 100%). $[\alpha]_D^{20}=+0.4$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.0–0.1 (m, 9H), 0.86, 0.88, 0.89 (3d, respectively, 3H, 3H, 6H, $J_1=J_2=J_3$=6.6 Hz), 0.9–1.1 (m, 2H), 1.07, 1.08 (2d, 6H, $J_1=J_2$=7.0 Hz), 1.17 (ddd, 1H, *J*=13.2, 8.2, 4.9 Hz), 1.34 (ddd, 1H, *J*=13.4, 8.3, 4.5 Hz), 1.4–1.8 (m, 12H), 1.8–2.0 (m, 4H), 2.47 (dq, 1H, *J*=8.0, 7.0 Hz), 2.49 (dq, 1H, *J*=8.0, 7.0 Hz), 2.72 (br s, 1H), 3.8–3.9 (m, 2H), 3.9–4.1 (m, 2H), 4.0–4.2 (m, 3H), 4.9–5.1 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.5 (3C), 13.1, 13.2, 17.2, 22.1, 22.3, 23.1, 23.2, 24.5, 24.5, 28.2, 28.5, 30.7, 31.4, 41.3, 41.6, 43.8, 45.3, 45.4, 46.4, 62.4, 66.9, 71.3, 76.5, 77.0, 80.1, 80.7, 174.2, 174.9; IR (film) 3520, 2956, 2870, 1732, 1464, 1384, 1368, 1336, 1251, 1189, 1167, 1062, 946, 901, 860, 838, 762, 694. Anal. Calcd for $C_{31}H_{58}O_7Si$: C, 65.22; H, 10.24. Found: C, 65.41; H, 10.41.

4.20. Tetramer 29

To a solution of acid **27** (116 mg, 0.20 mmol) and Et_3N (64 μL, 0.46 mmol) in THF (2.4 mL) was added, at room temperature, 2,4,6-trichlorobenzoyl chloride (53 μL, 0.34 mmol). The mixture was stirred at room temperature for 2 h. The white precipitate was filtered off under argon and washed with THF. The filtrate was evaporated under reduced pressure. The residue was diluted with CH_2Cl_2 (7 mL) and DMAP (73 mg, 0.60 mmol) was added at room temperature, followed by a solution of the alcohol **28** (92 mg, 0.16 mmol) in CH_2Cl_2 (2 mL). The resulting mixture was stirred overnight at room temperature, then quenched by adding a saturated solution of NH_4Cl. The aqueous layer was extracted twice with CH_2Cl_2 and the combined organic extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/AcOEt, 9/1 then CH_2Cl_2/MeOH, 98/2) to give the tetramer **29** as a colorless oil (161 mg, 90%). $[\alpha]_D^{20}=+7.8$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.0–0.1 (m, 9H), 0.87, 0.89, 0.90 (3d, respectively, 9H, 9H, 6H, $J_1=J_2=J_3$=6.6 Hz), 0.9–1.1 (m, 2H), 1.05, 1.06, 1.08, 1.09 (4d, 12H, $J_1=J_2=J_3=J_4$=7.1 Hz), 1.1–1.4 (m, 4H), 1.4–2.0 (m, 32H), 2.4–2.6 (m, 4H), 3.5–3.7 (m, 1H), 3.7–3.9 (m, 3H), 3.9–4.1 (m, 5H), 4.1–4.2 (m, 2H), 4.50 (s, 2H), 4.9–5.1 (m, 3H), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.6 (3C), 12.7, 12.8, 13.0 (2C), 17.1, 22.1, 22.2, 22.2, 22.8, 23.0, 23.0, 23.0, 23.0, 24.4 (3C), 24.5, 27.9, 28.0, 28.2 (2C), 31.3, 31.4 (2C), 31.5, 41.1, 41.1, 41.2, 41.6, 43.7 (3C), 44.3, 45.1, 45.1, 45.3, 45.6, 62.3, 70.8, 70.9, 71.0, 71.4, 75.3, 76.3, 76.5, 76.5, 76.6,

79.6, 79.7, 79.8, 80.0, 127.2, 127.6 (2C), 128.1 (2C), 138.8, 174.0, 174.1, 174.1, 174.8; IR (film) 3088, 3064, 3030, 2955, 2871, 1946, 1864, 1732, 1497, 1463, 1378, 1368, 1337, 1251, 1189, 1167, 1062, 945, 903, 859, 838, 736, 697. Anal. Calcd for $C_{64}H_{108}O_{13}Si$: C, 69.03; H, 9.78. Found: C, 68.93; H, 9.73.

4.21. Tetramer 30

To a solution of the ester **29** (155 mg, 0.14 mmol) in THF (1.5 mL) was added, at 0 °C, a 1 M solution of TBAF in THF (418 μL, 0.42 mmol). The mixture was stirred at 0 °C for 2 h and at room temperature overnight, then diluted with Et_2O (5 mL) and brine (5 mL). The phases were separated and the organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (cyclohexane/AcOEt, 8/2+AcOH, 1%) to give the acid **30** as a colorless oil (135 mg, 96%). $[\alpha]_D^{20}=+8.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.87, 0.88, 0.89, 0.89 (4d, respectively, 9H, 3H, 9H, 3H, $J_1=J_2=J_3=J_4=6.7$ Hz), 1.05, 1.07, 1.09 (3d, 9H, $J_1=J_2=J_3=7.1$ Hz), 1.14 (d, 3H, $J=7.1$ Hz), 1.1–1.4 (m, 4H), 1.4–2.1 (m, 32H), 2.4–2.6 (m, 4H), 3.5–3.7 (m, 1H), 3.7–3.9 (m, 2H), 3.9–4.1 (m, 6H), 4.50 (s, 2H), 4.9–5.1 (m, 3H), 7.2–7.4 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 13.0, 13.0 (2C), 22.0, 22.2 (2C), 22.8, 23.0, 23.0, 23.0, 23.0, 24.4 (3C), 24.5, 27.9, 28.1, 28.2, 28.7, 31.2, 31.3, 31.4, 31.5, 41.1, 41.1 (2C), 41.6, 43.6, 43.7 (2C), 44.3, 44.8, 45.1, 45.2, 45.6, 70.7, 70.9, 70.9, 71.4, 75.4, 76.4, 76.5, 76.5, 76.9, 79.6, 79.8, 79.9 (2C), 127.3, 127.7 (2C), 128.2 (2C), 138.8, 174.1, 174.2, 174.3, 178.3; IR (film) 3700–2200, 3089, 3064, 3030, 2955, 2871, 1732, 1463, 1368, 1261, 1191, 1168, 1142, 1063, 1029, 946, 904, 736, 698. Anal. Calcd for $C_{59}H_{96}O_{13}$: C, 69.93; H, 9.55. Found: C, 69.72; H, 9.29.

4.22. Tetramer 31

A mixture of the ether **30** (125 mg, 0.12 mmol) and 10% palladium on charcoal (30 mg) in MeOH (1.5 mL) was stirred for 4 h at room temperature under H_2 (1 atm). The solid was filtered off and washed with AcOEt. The filtrate was evaporated under reduced pressure. The residue was purified by flash chromatography (cyclohexane/AcOEt, 1/1 then cyclohexane/AcOEt, 1/2+AcOH, 1%) to give the hydroxy acid **31** as a colorless oil (82 mg, 72%). $[\alpha]_D^{20}=-11.0$ (*c* 0.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.86, 0.88, 0.88, 0.89 (4d, respectively, 9H, 6H, 3H, 6H, $J_1=J_2=J_3=J_4=6.7$ Hz), 1.05, 1.06, 1.08 (3d, 9H, $J_1=J_2=J_3=7.1$ Hz), 1.13 (d, 3H, $J=7.1$ Hz), 1.18 (ddd, 1H, $J=13.6$, 8.6, 3.2 Hz), 1.2–1.4 (m, 3H), 1.4–2.1 (m, 32H), 2.4–2.6 (m, 4H), 3.7–4.1 (m, 8H), 4.1–4.2 (m, 1H), 4.9–5.1 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.7, 13.0, 13.0, 13.2, 22.0, 22.1, 22.2, 22.3, 23.0 (2C), 23.0, 23.2, 24.5 (4C), 27.9, 28.1, 28.4, 28.6, 30.7, 31.2, 31.3, 31.4, 41.1, 41.1 (2C), 41.6, 43.7, 43.7, 43.7, 44.9, 45.1, 45.2, 45.4, 46.3, 66.9, 70.8, 70.9, 71.0, 76.4, 76.5, 76.8, 76.9, 79.7, 79.9, 79.9, 80.7, 174.2, 174.2, 174.4, 178.3; IR (film) 3700–2200, 2955, 2870, 1732, 1464, 1367, 1261, 1192, 1167, 1067, 902, 737, 696. Anal. Calcd for $C_{52}H_{90}O_{13}\cdot 0.54H_2O$: C, 66.94; H, 9.72. Found: C, 66.94; H, 9.45.

4.23. Macrotetrolide 32

To a mixture of hydroxy acid **31** (77 mg, 0.08 mmol), DMAP (69 mg, 0.57 mmol), and powered/activated molecular sieves (4 Å, 2.12 g) in CH_2Cl_2 (40 mL) was added slowly, at room temperature, 2,4,6-trichlorobenzoyl chloride (22 μL, 0.14 mmol). The mixture was stirred at the same temperature overnight, then the solids were filtered off and washed with CH_2Cl_2. The filtrate was washed with dilute HCl, aqueous $NaHCO_3$, and brine before being dried ($MgSO_4$). After removal of the solvent, the residue was chromatographed (cyclohexane/AcOEt, 7/3) to give the macrotetrolide **32** as a colorless oil (45 mg, 60%). $[\alpha]_D^{20}=0.0$ (*c* 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.88, 0.90 (2d, respectively, 12H, 12H, $J_1=J_2=6.6$ Hz), 1.07 (d, 12H, $J=7.0$ Hz), 1.31 (ddd, 4H, $J=13.6$, 8.2, 4.9 Hz), 1.4–1.7 (m, 16H), 1.69 (ddd, 4H, $J=13.7$, 6.8, 6.8 Hz), 1.77 (ddd, 4H, $J=13.7$, 6.5, 5.8 Hz), 1.8–2.0 (m, 4H), 1.9–2.1 (m, 4H), 2.56 (dq, 4H, $J=7.2$, 7.0 Hz), 3.82 (dddd, 4H, $J=6.7$, 6.7, 6.7, 6.7 Hz), 4.04 (ddd, 4H, $J=7.2$, 7.2, 7.0 Hz), 4.98 (dddd, 4H, $J=7.8$, 7.8, 5.4, 5.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5 (4C), 22.3 (4C), 23.0 (4C), 24.6 (4C), 27.8 (4C), 31.3 (4C), 40.8 (4C), 43.6 (4C), 44.6 (4C), 70.6 (4C), 76.1 (4C), 79.6 (4C), 174.4 (4C); IR (film) 2956, 2871, 1732, 1463, 1369, 1337, 1264, 1191, 1166, 1141, 1059; HRMS (FD) *m/z* $[M]^+$ Calcd for $C_{52}H_{88}O_{12}$: 904.6276, found: 904.6335.

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