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Total Synthesis of Pamamycin-649B

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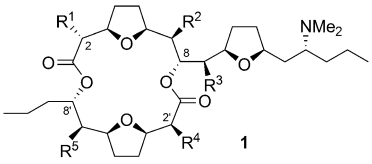
Dedicated to Professor Barry M. Trost on the occasion of his 70th birthday

Abstract: The first total synthesis of the macrodiolide antibiotic pamamycin-649B (**1**) was achieved by using sultone methodology. The diethyl substituted larger hydroxy acid fragment was constructed in a concise fashion through domino elimination/alkoxide-directed 1,6-additions of ethyllithium to sultones derived from intramolecular Diels–Alder reaction of furan-containing vinylsulfonates. Intermolecular Yamaguchi esterification of the two hydroxy acid building blocks and subsequent Yamaguchi cyclization eventually provided the target macrocycle **1**. Since the final lactonization with formation of the ester linkage between C1′ and the C8 oxygen proceeded with complete C2′ epimerization, the more readily available C2′ epimeric smaller fragment could be used to streamline the synthetic sequence.

Keywords: antibiotics · domino reactions · natural products · sulfur heterocycles · total synthesis

Introduction

The pamamycins (**1**) are structurally intriguing 16-membered macrodiolides isolated from various *Streptomyces* species that display a wide range of biological activities (Figure 1).[1] Next to possessing pronounced autoregulatory, anionophoric, and antifungal activities, several homologues have been shown to be highly active against Gram-positive bacteria including multiple antibiotic-resistant strains of *Mycobacterium tuberculosis*.[1a] More recent investigations on the antimycobacterial activity of pamamycin-607 (**1a**) on 25 independent *M. tuberculosis* clinical isolates (either susceptible, mono-, or multiresistant to the first line antituberculous drugs) established minimum inhibitory concentrations MIC_{100} in the range of 1.5–2.0 $\mu g\,mL^{-1}$, while the MIC_{100} of **1a** for a bioluminescent laboratory strain of *M. tuberculosis* (H37Rv) was determined as 0.55 $\mu g\,mL^{-1}$.[2a] Parallel studies on the effect of **1a** on the cell cycle distribution of human (HL-60) cells by flow cytometry indicated no (cell cycle) or only small effects (apoptosis) at the latter concentration.[2b] Thus, **1a** might emerge as a promising lead molecule for the development of novel antituberculous drugs.



	R^1	R^2	R^3	R^4	R^5	pamamycin
1a	Me	Me	Me	Me	H	607
1b	Me	Me	Me	Me	Me	621A
1c	Me	Me	Me	Et	Me	635B
1d	Et	Me	Et	Me	H	635F
1e	Et	Me	Et	Et	H	649A
1f	Et	Me	Et	Me	Me	649B

Figure 1. Selected pamamycin homologues.

Due to their biological properties and unique structure, the pamamycin macrodiolides have stimulated considerable synthetic efforts,[3,4] and the total syntheses of pamamycin-607 (**1a**),[5] pamamycin-621A (**1b**),[6] and pamamycin-635B (**1c**) have been achieved.[6a] Our approach to **1a** was based on the extensive application of sultone chemistry.[3a,5c] The synthetic route developed in this context proved to be quite general, since modification of the smaller hydroxy acid fragment allowed an efficient access to the homologues **1b** and **1c** as well.[6a] Here we report the first total synthesis of the higher homologue pamamycin-649B (**1f**)[7] by modification of the larger hydroxy acid fragment.

Results and Discussion

Retrosynthetic disconnection of **1f** led to the silylated larger hydroxy acid **2** that also occurs in pamamycin-635F (**1d**) and -649A (**1e**) as well as to the benzyl ester **3** or its C2′ epimer **4** (Scheme 1). Since the more readily available C2′ epimeric smaller fragment **4** had previously been used successfully in a streamlined total synthesis of pamamycin-621A (**1b**),[6a] we felt that it could also be applied to a corresponding shortened access to pamamycin-649B (**1f**).

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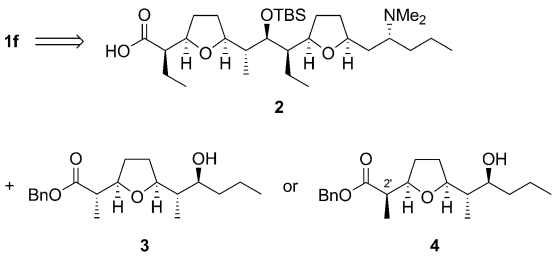


Scheme 1. Retrosynthetic analysis of **1f**. TBS = *tert*-butyldimethylsilyl.

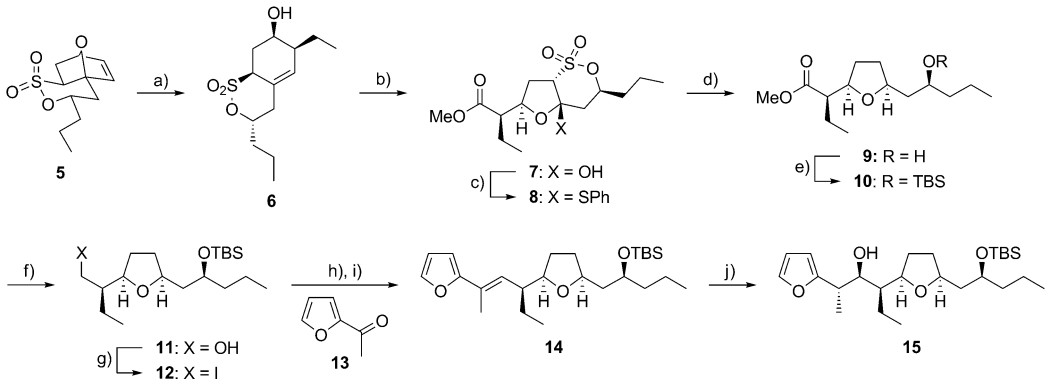
Sultone **5** that already served as a building block for the pamamycins **1a–c**,[3a,5c,6a] was treated with two equivalents of ethyllithium, which induced a domino elimination/alkoxide-directed 1,6-addition to yield the bicyclic compound **6** (Scheme 2). Ozonolysis of this cyclohexene followed by eliminative workup at reflux in dichloromethane afforded a single hemiacetal **7**. Lewis-acid-catalyzed exchange of the hydroxyl group in **7** against a phenylthio group in **8** proceeded with retention of configuration as proven by X-ray diffraction analysis.[8] Subjecting thioether **8** to a domino reductive elimination/hydrogenation with Raney nickel under hydrogen pressure gave alcohol **9**.[6a,9] Silylation followed by ester reduction and iodide substitution then delivered the iodide **12**. Halogen–lithium exchange of **12**, addition of the resultant organolithium intermediate to 2-acetylfuran (**13**), and brief exposure of the alcohols thus formed to catalytic amounts of concentrated aqueous hydrogen chloride smoothly yielded the (*E*)-olefin **14**. Diastereoselective hydroboration/oxidation of **14** gave largely the desired stereoisomer **15** due to minimization of allylic 1,3-strain.[10,11]

The second iterative cycle of our sultone route commenced with a domino esterification/cycloaddition by reacting hydroxyalkylfuran **15** with vinylsulfonyl chloride (Scheme 3).[10] The resultant single sultone **16** gave suitable crystals for X-ray diffraction analysis.[8] Domino elimination/alkoxide-directed 1,6-addition by treatment of **16** with two equivalents of ethyllithium afforded the cyclohexene **17**. Ozonolysis of **17** with eliminative workup at elevated temperature and treatment of the intermediate hemiacetal **18** with thiophenol in the presence of trifluoroborane not only effected lactol *S*,*O*-acetal interchange, but simultaneously cleaved the silyl ether on the side chain to give alcohol **19** with complete diastereoselectivity. Subjecting **19** to a Mitsunobu reaction with hydrazoic acid delivered azide **20** nearly quantitatively. Subsequent treatment of **20** with Raney nickel under hydrogen pressure followed by addition of an aqueous formaldehyde solution to the reaction mixture caused desulfurization via domino reductive elimination/hydrogenation, azide reduction, and twofold reductive N-methylation to provide alcohol **21**.[12] Silylation of **21** then yielded TBS ether **22** as a single stereoisomer.

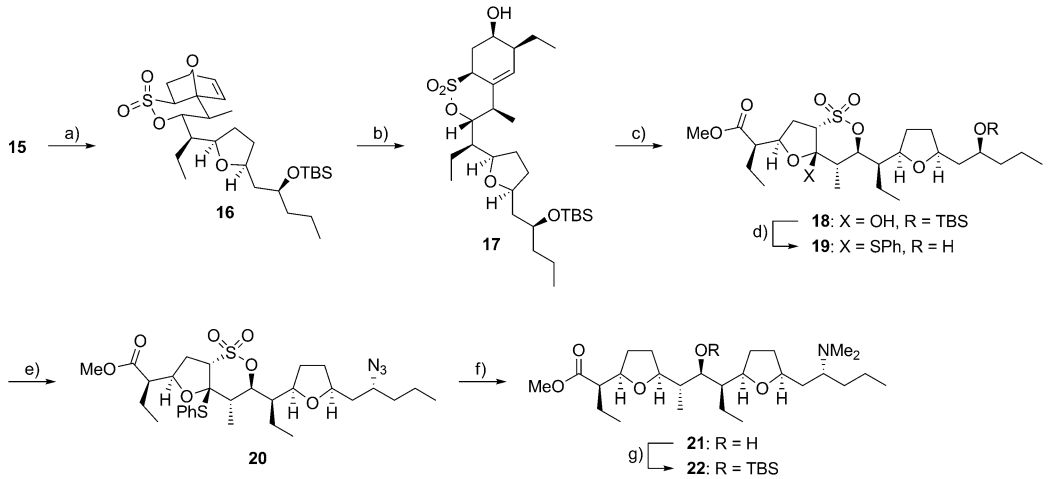
Mild saponification of methyl ester **22** yielded the larger fragment coupling component **2** (Scheme 4). The total synthesis of **1f** was then completed using the C2′ epimeric smaller fragment benzyl ester **4**. Intermolecular Yamaguchi esterification[13] of **2** with **4** at reflux in toluene efficiently provided coupling product **23**. Desilylation of **23** and reductive debenzylation of the resulting benzyl ester **24** proceeded uneventfully to give *seco*-acid **25**. Finally, modified Yamaguchi cyclization of **25** (0.7×10^{-3} M) under Fleming conditions[14] afforded pamamycin-649B (**1f**) as the single macrodiolide product in good yield.[15] Thus, as has been observed during the total syntheses of the homologues **1a–c**,[3a,6a] the final Yamaguchi lactonization with formation of the ester linkage between C1′ and the C8 oxygen proceeded with complete C2′ epimerization.

Conclusion

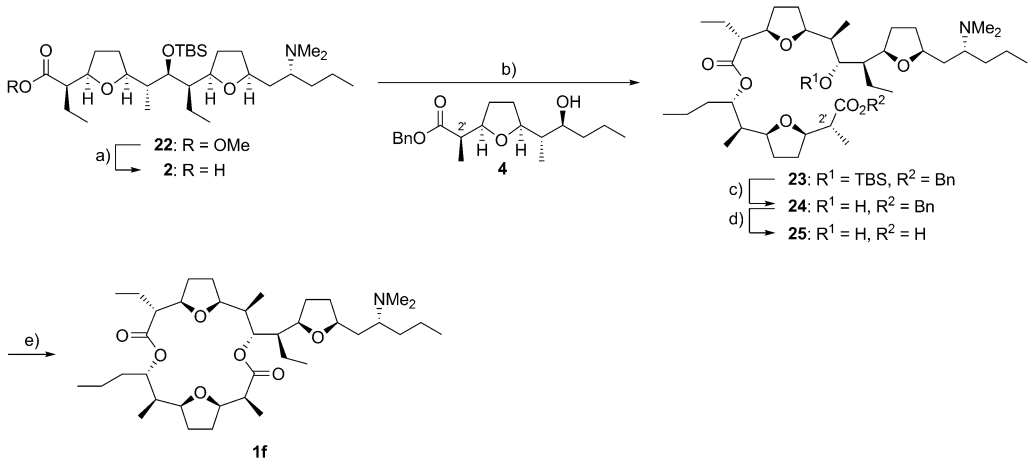
In conclusion, a short and highly stereoselective access to the silylated larger hydroxy acid **2** of the pamamycins **1d–f** has been developed by application of sultone methodology. Subsequent coupling of **2** with the smaller fragment surro-



Scheme 2. Sultone route to hydroxy ester **9** and its elaboration to hydroxyalkylfuran **15**. a) 1) 2 equiv EtLi, THF, Et_2O, hexane, −78 °C → RT, 2) NH_4Cl, H_2O, 36%; b) 1) O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −78 °C, 2) Ac_2O, pyridine, CH_2Cl_2, RT → reflux, 87%; c) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → RT, 78%; d) Raney Ni (W2), 50 bar H_2, EtOH, RT, 45%; e) TBSCl, imidazole, DMAP, DMF, RT, 98%; f) $LiAlH_4$, Et_2O, 0 °C → RT, 97%; g) I_2, Ph_3P, imidazole, Et_2O, MeCN, RT, 99%; h) 1) *t*BuLi, Et_2O, hexane, −78 °C, 2) **13**, MS 4 Å, −78 °C → RT; i) conc. aq. HCl, CH_2Cl_2, RT, 71% from **12**; j) 1) $BH_3{\cdot}THF$, THF, 0 °C → RT, 2) 30% aq. H_2O_2, NaOH, 0 °C → RT, 51%. DMAP = 4-(*N*,*N*-dimethylamino)pyridine, MS = molecular sieves.



Scheme 3. Sultone route to the protected larger fragment **22**. a) CH_2=$CHSO_2Cl$, Et_3N, THF, 0 °C → RT, 88 %; b) 1) 2 equiv EtLi, THF, Et_2O, hexane, −78 °C → RT, 2) NH_4Cl, H_2O, 58 %; c) 1) O_3, $NaHCO_3$, CH_2Cl_2, MeOH, −78 °C, 2) Ac_2O, pyridine, CH_2Cl_2, 0 °C → reflux, 78 %; d) PhSH, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C → RT, 76 %; e) HN_3, DIAD, Ph_3P, toluene, 0 °C → RT, 98 %; f) 1) Raney Ni (W2), 50 bar H_2, EtOH, RT, 2) 37 % aq. CH_2O, 50 bar H_2, RT; g) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C → RT, 47 % from **20**. DIAD = diisopropyl azodicarboxylate.



Scheme 4. Final steps of the synthesis of pamamycin-649B (**1f**). a) LiOH, THF, MeOH, RT, 41 % (77 % based on recovered starting material); b) 1) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, RT, 2) **4**, DMAP, toluene, reflux, 80 %; c) 40 % aq. HF, MeCN, RT, 91 %; d) H_2, 10 % Pd/C, THF, RT; e) 2,4,6-trichlorobenzoyl chloride, DMAP, MS 4 Å, CH_2Cl_2, RT, 53 % from **24**.

gate **4** enabled the first total synthesis of pamamycin-649B (**1f**). Further biological evaluation of the pamamycins is ongoing and will be reported in due course.

Experimental Section

General: All reactions requiring exclusion of moisture were run under argon using flame-dried glassware. Solvents were dried by distillation from Na/K and benzophenone (THF), Na (toluene) or CaH_2 (CH_2Cl_2). All commercially available compounds were used as received unless stated otherwise. $MgSO_4$ was generally utilized for drying after extractive work-up. Flash chromatography: Merck silica gel 60 (40–63 μm). Thin-layer chromatography: Merck silica gel 60 F_{254} plates. Melting points: Kleinfeld Labortechnik Electrothermal IA 9100 apparatus. Optical rotation: Perkin–Elmer 341 polarimeter. ^1H and ^{13}C NMR: Bruker DRX-500 (^1H: 500 MHz, ^{13}C: 126 MHz), calibrated to the residual resonance of the solvent or TMS. FT-IR: Nicolet Avatar 360 spectrometer. Mass spectra: Agilent 5973N detector coupled with an Agilent 6890N GC (GC/MS, 70 eV) or else Bruker Esquire-LC (direct injection as a methanolic NH_4OAc solution, ESI). Exact mass: Finnigan MAT 95. Elemental analysis: Hekatech EA 3000. X-Ray: Bruker Kappa CCD diffractometer.

Cyclohexene 6: To generate EtLi, freshly distilled EtI (0.50 mL, 6.19 mmol) was dissolved in Et_2O (15 mL) and *t*BuLi (1.5 M solution in hexane, 8.60 mL, 12.9 mmol) was added to this solution at −78 °C. After stirring for 1 h at this temperature and additional 2 h at room temperature, the resulting suspension was added dropwise to a solution of **5** (500 mg, 2.05 mmol) in THF (55 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and then for 1 h at room temperature. Subsequently, it was quenched with saturated aqueous NH_4Cl solution (10 mL), and the aqueous layer was extracted with Et_2O (4×10 mL). The combined organic layers were dried and filtered. After removal of the solvent and purification by flash chromatography (CH_2Cl_2/Et_2O 6:1), cyclohexene **6** (215 mg, 36 %) was isolated as a white solid. R_f = 0.35 (CH_2Cl_2/Et_2O 6:1); m.p. 47 °C; $[\alpha]_D^{25}$ = −34.9 (c = 0.90 in CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91–0.94 (m, 6H), 1.26–1.34 (m, 1H),

1.38–1.61 (m, 3H), 1.65–1.77 (m, 2H), 2.09–2.18 (m, 2H), 2.30–2.35 (m, 2H), 2.39–2.45 (m, 2H), 3.52–3.58 (m, 1H), 3.82–3.85 (m, 1H), 4.52–4.57 (m, 1H), 5.71–5.72 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 10.68 (q), 13.53 (q), 17.93 (t), 24.44 (t), 28.85 (t), 36.73 (t), 38.74 (t), 44.47 (d), 59.25 (d), 68.10 (d), 84.76 (d), 126.20 (s), 131.96 ppm (d); IR (KBr): ν = 3224 (broad), 2960, 2934, 2874, 1459, 1432, 1352, 1337, 1289, 1216, 1199, 1166, 1137, 1118, 1069, 1015, 961, 936, 893, 880, 819, 802, 785, 734, 682, 619 cm^{-1}; MS (GC/MS, 70 eV): m/z (%): 166 (100) $[M-CH_3CHO-SO_2]^+$; elemental analysis calcd (%) for $C_{13}H_{22}O_4S$: C 56.91, H 8.08, S 11.69; found: C 57.03, H 8.12, S 11.50.

Hemiacetal 7: Cyclohexene **6** (3.71 g, 12.9 mmol) was dissolved in CH_2Cl_2 (80 mL) and MeOH (25 mL), and $NaHCO_3$ (3.66 g, 43.6 mmol) were added. This suspension was ozonized at −78 °C until a constant blue coloration was reached. To remove excessive ozone, the reaction mixture was purged with N_2. Subsequently, the mixture was allowed to reach room temperature. $NaHCO_3$ was filtered off, and the solvent was evaporated at 30 °C. The residue was at first dissolved in THF (10 mL) and after evaporation of the solvent dissolved again in CH_2Cl_2 (30 mL). Pyridine (2.08 mL, 25.7 mmol) and Ac_2O (1.22 mL, 12.9 mmol) were added, and the resulting solution was stirred for 12 h at room temerature and further 12 h under reflux. Thereafter it was diluted with Et_2O (200 mL) and washed with 1 N HCl (75 mL) and saturated aqueous $NaHCO_3$ solution (75 mL). The organic layer was then dried and the solvent removed at 30 °C. Final purification by flash chromatography (pentane/EtOAc 3:1) gave **7** (3.78 g, 87%) as a colorless oil. R_f = 0.39 (pentane/EtOAc 1:1); $[\alpha]_D^{25}$ = −28.6 (c = 1.15 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.91–0.96 (m, 6H), 1.37–1.43 (m, 1H), 1.51–1.60 (m, 3H), 1.66–1.74 (m, 2H), 2.04–2.07 (m, 1H), 2.21 (m, 1H), 2.36–2.41 (m, 1H), 2.48–2.53 (m, 1H), 2.65–2.69 (m, 1H), 3.61 (d, J = 7.3 Hz, 1H), 3.72 (s, 3H), 4.34 (s, 1H), 4.57–4.58 (m, 1H), 4.66–4.68 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.80 (q), 13.54 (q), 17.97 (t), 22.79 (t), 29.83 (t), 36.22 (t), 39.65 (t), 51.99 (q), 54.06 (d), 65.72 (d), 80.42 (d), 80.49 (d), 104.36 (s), 175.21 ppm (s); IR (neat): ν = 3458 (broad), 2963, 2877, 1734, 1710, 1437, 1358, 1257, 1208, 1170, 1096, 1037, 985, 885, 808, 750, 625 cm^{-1}; MS (ESI): m/z: 354.2 $[M+NH_4]^+$.

***S*,*O*-Acetal 8**: To a solution of **7** (2.37 g, 7.05 mmol) in CH_2Cl_2 (20 mL) thiophenol (4.68 mL, 45.8 mmol) and $BF_3{\cdot}Et_2O$ (1.03 mL, 8.10 mmol) were added at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with CH_2Cl_2 (4 × 10 mL), and the combined organic layers were dried and filtered. After evaporation of the solvent, the residue was purified by flash chromatography (pentane/EtOAc 9:1) to afford **8** (2.37 g, 78%) as a colorless oil. R_f = 0.16 (pentane/EtOAc 9:1); $[\alpha]_D^{25}$ = +37.3 (c = 0.95 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.1 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H), 1.31–1.36 (m, 1H), 1.40–1.47 (m, 2H), 1.52–1.64 (m, 3H), 2.13–2.15 (m, 2H), 2.59–2.65 (m, 1H), 2.79–2.83 (m, 1H), 2.93–2.98 (m, 1H), 3.77 (s, 3H), 3.82 (d, J = 7.1 Hz, 1H), 4.64–4.67 (m, 1H), 4.84–4.89 (m, 1H), 7.33–7.41 (m, 3H), 7.55–7.57 ppm (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.46 (q), 13.42 (q), 17.85 (t), 22.33 (t), 31.93 (t), 36.16 (t), 39.98 (t), 51.64 (q), 54.59 (d), 65.27 (d), 81.40 (d), 82.70 (d), 95.25 (s), 129.19 (d), 129.65 (d), 130.02 (s), 136.17 (d), 174.09 ppm (s); IR (neat): ν = 3051, 2875, 1734, 1459, 1439, 1364, 1308, 1269, 1255, 1202, 1167, 1086, 1068, 1022, 985, 929, 889, 832, 807, 751, 692, 620, 553 cm^{-1}; MS (ESI): m/z: 446.0 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{20}H_{28}O_6S_2$: C 56.05, H 6.59, S 14.96; found: C 56.12, H 6.62, S 14.88.

Hydroxy ester 9: To a Raney Ni suspension [freshly prepared from Al/Ni alloy (38.0 g) and NaOH (31.0 g, 775 mmol)] in EtOH (80 mL) *S*,*O*-acetal **8** (3.77 g, 8.80 mmol) was added. The mixture was stirred for 24 h under H_2 (50 bar) at room temperature. Then the suspension was filtered over a frit, and the filtration residue was washed with THF (3 × 100 mL). The solvent was removed, and the crude product was purified by flash chromatography (CH_2Cl_2/EtOAc 4:1). Hydroxy ester **9** (1.02 g, 45%) was isolated as a colorless liquid. R_f = 0.11 (CH_2Cl_2/EtOAc 4:1); $[\alpha]_D^{25}$ = −12.1 (c = 1.06 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.86 (t, J = 7.4 Hz, 3H), 0.89 (t, J = 7.1 Hz, 3H), 1.30–1.49 (m, 5H), 1.57–1.64 (m, 4H), 1.67–1.72 (m, 1H), 1.94–2.00 (m, 2H), 2.29–2.34 (m, 1H), 2.61 (br s, 1H), 3.67 (s, 3H), 3.76–3.80 (m, 1H), 3.90–3.94 (m, 1H), 4.09–4.11 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 11.84 (q), 14.07 (q), 18.94 (t), 22.36 (t), 29.45 (t), 30.39 (t), 39.32 (t), 40.95 (t), 51.50 (q), 53.69 (d), 68.66 (d), 76.75 (d), 80.54 (d), 174.77 ppm (s); IR (neat): ν = 3449 (broad), 2957, 2935, 2873, 1736, 1460, 1435, 1378, 1348, 1270, 1238, 1196, 1176, 1160, 1076, 1025, 997, 905, 846, 798, 748, 671, 621, 577, 552 cm^{-1}; MS (ESI): m/z: 241.3 $[M-H_2O+H]^+$, 259.2 $[M+H]^+$, 276.2 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{14}H_{26}O_4$: C 65.09, H 10.14; found: C 64.90, H 10.36.

Silylether 10: Imidazole (671 mg, 9.86 mmol), DMAP (482 mg, 3.95 mmol) and TBSCl (1.19 g, 7.89 mmol) were added to a solution of **9** (1.02 g, 3.95 mmol) in DMF (30 mL). After stirring for 3 h at room temperature, the reaction was quenched with water (50 mL), and Et_2O (40 mL) was added. The aqueous layer was extracted with Et_2O (3 × 50 mL), and then the combined organic layers were washed with 2 N HCl (50 mL) and saturated aqueous $NaHCO_3$ solution (50 mL), dried and filtered. Purification by flash chromatography (pentane/Et_2O 5:1) gave **10** (1.44 g, 98%) as a colorless liquid. R_f = 0.48 (pentane/Et_2O 5:1); $[\alpha]_D^{25}$ = +19.1 (c = 1.44 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.01 (s, 6H), 0.08–0.90 (m, 15H), 1.27–1.33 (m, 2H), 1.37–1.60 (m, 8H), 1.91–1.95 (m, 2H), 2.25–2.30 (m, 1H), 3.67 (s, 3H), 3.68–3.80 (m, 1H), 3.85–3.90 ppm (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.76 (q), −4.58 (q), 11.91 (q), 14.34 (q), 17.98 (t), 18.10 (s), 22.27 (t), 25.94 (q), 29.40 (t), 31.33 (t), 40.49 (t), 43.42 (t), 51.32 (q), 54.07 (d), 69.53 (d), 75.91 (d), 79.84 (d), 174.78 ppm (s); IR (neat): ν = 2955, 2934, 2857, 1740, 1462, 1434, 1380, 1252, 1195, 1177, 1154, 1076, 1038, 1005, 946, 920, 834, 808, 774, 663 cm^{-1}; MS (ESI): m/z: 373.1 $[M+H]^+$; elemental analysis calcd (%) for $C_{20}H_{40}O_4Si$: C 64.47, H 10.82; found: C 64.68, H 10.92.

Alcohol 11: To a suspension of $LiAlH_4$ (185 mg, 4.88 mmol) in Et_2O (50 mL) a solution of **10** (1.21 g, 3.25 mmol) in Et_2O (25 mL) was added dropwise at 0 °C. The reaction mixture was stirred for 1 h at room temperature. Then it was quenched with water (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) after addition of 2 N HCl (pH 1). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution, dried, filtered, and evaporated. Final purification by flash chromatography (pentane/Et_2O 1:1) afforded **11** (1.09 g, 97%) as a colorless liquid. R_f = 0.51 (pentane/Et_2O 1:1); $[\alpha]_D^{25}$ = +44.5 (c = 1.28 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.03 (s, 6H), 0.82–0.93 (m, 15H), 1.16–1.23 (m, 1H), 1.26–1.49 (m, 7H), 1.55–1.61 (m, 3H), 1.90–2.02 (m, 2H), 3.12 (br s, 1H), 3.57–3.61 (m, 1H), 3.66–3.71 (m, 1H), 3.73–3.79 (m, 2H), 3.90–3.93 ppm (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = −4.86 (q), −4.43 (q), 11.72 (q), 14.30 (q), 17.97 (t), 18.10 (s), 21.64 (t), 25.89 (q), 30.45 (t), 30.97 (t), 40.52 (t), 43.15 (t), 47.29 (d), 65.39 (t), 69.46 (d), 76.34 (d), 84.45 ppm (d); IR (neat): ν = 3464 (broad), 2956, 2930, 2857, 1463, 1379, 1252, 1039, 1006, 940, 834, 807, 773, 663, 583, 570 cm^{-1}; MS (ESI): m/z: 345.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{40}O_3Si$: C 66.22, H 11.70; found: C 66.26, H 11.74.

Iodide 12: Alcohol **11** (642 mg, 1.86 mmol) was dissolved in Et_2O (25 mL) and MeCN (10 mL). Imidazole (216 mg, 3.17 mmol), Ph_3P (735 mg, 2.80 mmol) and I_2 (709 mg, 2.79 mmol) were added successively. After stirring for 1 h at room temperature, the reaction was quenched with water (25 mL), and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ solution (25 mL), dried and filtered. The filtrate was evaporated, and purification of the residue was achieved by flash chromatography (pentane/Et_2O 10:1) to give **12** (837 mg, 99%) as a colorless liquid. R_f = 0.66 (pentane/Et_2O 10:1); $[\alpha]_D^{25}$ = +9.4 (c = 1.92 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.05 (s, 3H), 0.06 (s, 3H), 0.85–0.90 (m, 15H), 0.94–0.95 (m, 1H), 1.26–1.34 (m, 3H), 1.40–1.44 (m, 4H), 1.51–1.54 (m, 3H), 1.93–1.96 (m, 2H), 3.38–3.40 (m, 1H), 3.50–3.51 (m, 1H), 3.54–3.57 (m, 1H), 3.82–3.88 ppm (m, 2H); ^{13}C NMR (75.5 MHz, $CDCl_3$,): δ = −4.48 (q), −4.42 (q), 10.59 (q), 13.19 (t), 14.38 (q), 18.01 (t), 18.14 (s), 23.56 (t), 25.98 (q), 29.17 (t), 31.63 (t), 40.53 (t), 43.51 (t), 45.86 (d), 69.57 (d), 75.53 (d), 80.56 ppm (d); IR (neat): ν = 2956, 2930, 2856, 1462, 1420, 1379, 1309, 1253, 1191, 1065, 1038, 1005, 945, 911, 834, 806, 773, 663 cm^{-1}; MS (ESI): m/z: 455.0 $[M+H]^+$; elemental analysis calcd (%) for $C_{19}H_{39}IO_2Si$: C 50.21, H 8.65; found: C 50.33, H 8.70.

Olefin 14: To a solution of **12** (1.58 g, 3.48 mol) in Et_2O (60 mL) *t*BuLi (1.5 M in hexane, 5.10 mL, 7.65 mmol) was added at −78 °C. After stirring

for 1 h at this temperature, a suspension of 2-acetylfuran (**13**) (574 mg, 5.21 mmol) and molecular sieves 4 Å (500 mg) in Et_2O (30 mL) was added dropwise. The mixture was allowed to stir for 12 h at room temperature before it was diluted with Et_2O (60 mL) and then quenched with saturated aqueous $NaHCO_3$ solution (60 mL). The aqueous layer was extracted with Et_2O (2×50 mL), acidified with 2 N HCl and extracted again with Et_2O (2×50 mL). Then the combined organic layers were dried, the solvent was removed by evaporation, the residue was dissolved in CH_2Cl_2 (50 mL), and concentrated aqueous HCl (1 drop) was added. This solution was stirred for 1 h at room temperature and then treated with saturated aqueous $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL), and the combined organic layers were dried and evaporated. Final purification by flash chromatography (pentane/CH_2Cl_2 5:1) gave **14** (1.04 g, 71% from **12**) as a colorless liquid. R_f=0.14 (pentane/CH_2Cl_2 5:1); $[\alpha]_D^{25}=+30$ (c=1.25 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.01 (s, 3H), 0.03 (s, 3H), 0.85–0.90 (m, 15H), 1.31–1.44 (m, 6H), 1.51–1.64 (m, 4H), 1.83–1.92 (m, 2H), 1.91 (s, 3H), 2.41 (m, 1H), 3.80–3.86 (m, 3H), 5.92–5.94 (m, 1H), 6.17 (d, J= 3.3 Hz, 1H), 6.35–6.36 (m, 1H), 7.30 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=−4.70 (q), −4.58 (q), 12.12 (q), 13.98 (q), 14.37 (q), 18.08 (t), 18.14 (s), 24.99 (t), 25.97 (q), 28.67 (t), 31.74 (t), 40.49 (t), 43.36 (t), 44.59 (d), 69.81 (d), 75.63 (d), 81.57 (d), 104.27 (d), 110.90 (d), 125.71 (s), 126.99 (d), 140.95 (d), 156.36 ppm (s); IR (neat): ν=2956, 2931, 2858, 1741, 1492, 1462, 1378, 1252, 1064, 1040, 1007, 947, 913, 833, 807, 773, 728, 675, 594 cm^{-1}; MS (ESI): m/z: 421.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{25}H_{44}O_3Si$: C 71.37, H 10.54; found: C 71.39, H 10.47.

Alcohol 15: Olefin **14** (875 mg, 2.08 mmol) was dissolved in THF (15 mL) and BH_3·THF (1 M in THF, 4.16 mL, 4.16 mmol) was added dropwise at 0 °C. After stirring for 3 h at 0 °C and further 3 h at room temperature, water (0.7 mL), 2 N NaOH (7.0 mL), and aqueous H_2O_2 solution (30%, 7.0 mL) were added carefully at 0 °C. The mixture was stirred for 1 h at room temperature, and then aqueous saturated $Na_2S_2O_3$ solution (33 mL) was added. The separated aqueous layer was extracted with Et_2O (3×30 mL), and the combined organic layers were dried, filtered, and evaporated. Purification by flash chromatography (pentane/EtOAc 10:0.5) gave **15** (465 mg, 51%) as a colorless liquid. R_f=0.23 (pentane/EtOAc 10:0.5); $[\alpha]_D^{25}=+34.9$ (c=1.18 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.02 (s, 6H), 0.83–0.87 (m, 12H), 0.98 (t, J= 7.5 Hz, 3H), 1.17 (d, J=7.1 Hz, 3H), 1.24–1.29 (m, 2H), 1.35–1.38 (m, 2H), 1.48–1.50 (m, 2H), 1.54–1.59 (m, 4H), 1.68–1.76 (m, 1H), 1.96–1.99 (m, 2H), 3.04–3.07 (m, 1H), 3.43 (brs, 1H), 3.78–3.80 (m, 2H), 4.02–4.03 (m, 2H), 6.10 (d, J=3.1 Hz, 1H), 6.30–6.31 (m, 1H), 7.32–7.33 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=−4.83 (q), −4.46 (q), 12.60 (q), 14.35 (q), 16.44 (q), 17.86 (t), 18.11 (s), 18.18 (t), 25.96 (q), 28.83 (t), 31.68 (t), 36.83 (d), 40.53 (t), 42.89 (t), 44.82 (d), 69.45 (d), 73.84 (d), 76.15 (d), 80.03 (d), 104.97 (d), 110.07 (d), 140.72 (d), 158.63 ppm (s); IR (neat): ν=3413 (broad), 2956, 2930, 2856, 1506, 1463, 1378, 1255, 1149, 1071, 1039, 1006, 946, 884, 834, 805, 774, 726, 663, 618, 599, 580 cm^{-1}; MS (ESI): m/z: 421.2 $[M-H_2O+H]^+$, 439.2 $[M+H]^+$; elemental analysis calcd (%) for $C_{25}H_{46}O_4Si$: C 68.44, H 10.57; found: C 68.79, H 10.63.

Sultone 16: Alcohol **15** (538 mg, 1.23 mmol) and Et_3N (0.68 mL, 4.91 mmol) were dissolved in THF (12 mL), and vinylsulfonyl chloride (0.22 mL, 2.43 mmol) was added at 0 °C. The reaction mixture was stirred for 12 h at room temperature and then quenched with ice water (10 mL). The aqueous layer was extracted with CH_2Cl_2 (10 mL), and the combined organic layers were washed with 2 N HCl (9 mL) and saturated aqueous $NaHCO_3$ solution (9 mL). After drying, filtration, and evaporation, the crude product was purified by flash chromatography (CH_2Cl_2). Sultone **16** (571 mg, 88%) was isolated as colorless crystals. R_f=0.16 (CH_2Cl_2); m.p. 117 °C; $[\alpha]_D^{25}=-5.1$ (c=1.23 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.03 (s, 3H), 0.05 (s, 3H), 0.85–0.90 (m, 12H), 0.99–1.06 (m, 6H), 1.28–1.32 (m, 2H), 1.38–1.52 (m, 5H), 1.58–1.65 (m, 3H), 1.72–1.82 (m, 2H), 1.95–1.99 (m, 2H), 2.51–2.61 (m, 2H), 3.11–3.13 (m, 1H), 3.81–3.89 (m, 3H), 5.01–5.03 (m, 1H), 5.17–5.19 (m, 1H), 6.03 (d, J=5.6 Hz, 1H), 6.52 ppm (dd, J=1.6 Hz, J=5.6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=−4.58 (q), −4.52 (q), 12.24 (q), 13.87 (q), 14.32 (q), 17.58 (t), 18.03 (t), 18.09 (s), 25.97 (q), 29.10 (t), 30.12 (t), 31.87 (t), 33.86 (d), 40.50 (t), 43.68 (t), 45.33 (d), 57.50 (d), 69.86 (d), 75.70 (d), 78.58 (d), 78.96 (d), 85.58 (d), 92.26 (s), 135.78 (d), 139.72 ppm (d); IR (KBr): ν=2935, 2859, 1462, 1356, 1346, 1317, 1296, 1250, 1166, 1133, 1065, 1044, 1009, 994, 948, 914, 892, 828, 772, 740, 712, 657, 631, 611 cm^{-1}; MS (ESI): m/z: 529.2 $[M+H]^+$, 546.2 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{27}H_{48}O_6SSi$: C 61.32, H 9.15, S 6.06; found: C 60.94, H 8.94, S 6.34.

Cyclohexene 17: To generate EtLi, freshly distilled EtI (255 μL, 3.19 mmol) was dissolved in Et_2O (7 mL), and tBuLi (1.5 M solution in hexane, 4.33 mL, 6.49 mmol) was added to this solution at −78 °C. After stirring for 1 h at this temperature and additional 1.5 h at room temperature, the resulting suspension was added dropwise to a solution of **16** (563 mg, 1.06 mmol) in THF (15 mL) at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and than for 1 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL), and the aqueous layer was extracted with Et_2O (4×10 mL). The combined organic layers were dried and filtered. After removal of the solvent and purification by flash chromatography (pentane/EtOAc 3:2), cyclohexene **17** (343 mg, 58%) was isolated as a white solid. R_f=0.36 (pentane/EtOAc 3:2); $[\alpha]_D^{25}=-27.6$ (c=1.21 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.02 (s, 3H), 0.03 (s, 3H), 0.81–0.91 (m, 12H), 1.00–1.03 (m, 6H), 1.10 (d, J=6.8 Hz, 3H), 1.24–1.33 (m, 2H), 1.35–1.56 (m, 8H), 1.58–1.75 (m, 3H), 1.93–1.99 (m, 2H), 2.01–2.19 (m, 1H), 2.13–2.19 (m, 1H), 2.62–2.68 (m, 2H), 3.14 (brs, 1H), 3.77–3.89 (m, 4H), 3.96 (m, 1H), 4.71–4.74 (m, 1H), 5.29–5.67 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=−4.65 (q), −4.62 (q), 11.63 (q), 12.62 (q), 13.64 (q), 14.32 (q), 17.93 (t), 18.03 (t), 18.08 (s), 24.00 (t), 25.94 (q), 27.66 (t), 29.68 (t), 31.79 (t), 37.99 (d), 40.45 (t), 41.77 (d), 43.72 (t), 46.49 (d), 59.06 (d), 63.94 (d), 69.68 (d), 75.41 (d), 78.30 (d), 90.29 (d), 129.74 (d), 130.20 ppm (s); IR (KBr): ν=3519 (broad), 2956, 2933, 2875, 2856, 1352, 1254, 1207, 1171, 1158, 1068, 1005, 924, 887, 835, 808, 774, 645, 605 cm^{-1}; MS (ESI): m/z: 559.2 $[M+H]^+$, 576.3 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{29}H_{54}O_6SSi$: C 62.32, H 9.74, S 5.74; found: C 62.48, H 9.82, S 5.38.

***S,O*-Acetal 19**: Cyclohexene **17** (343 mg, 0.61 mmol) was dissolved in CH_2Cl_2 (30 mL), and MeOH (10 mL) and $NaHCO_3$ (390 mg, 4.64 mmol) was added. This suspension was ozonized at −78 °C until a constant blue coloration was reached. To remove excessive ozone, the reaction mixture was purged with N_2. Subsequently, the mixture was allowed to reach room temperature. $NaHCO_3$ was filtered off and rinsed with CH_2Cl_2 (20 mL). Then the solvent was evaporated at 30 °C. The residue was at first dissolved in THF (10 mL) and after evaporation of the solvent dissolved again in CH_2Cl_2 (20 mL). Pyridine (98 μL, 1.21 mmol) and Ac_2O (58 μL, 0.61 mmol) were added at 0 °C, and the resulting solution was stirred for 12 h at room temperature and further 12 h at reflux. Thereafter it was diluted with Et_2O (130 mL) and washed with 1 N HCl (20 mL) and saturated aqueous $NaHCO_3$ solution (20 mL). The organic layer was then dried and the solvent removed at 30 °C. Purification by flash chromatography (pentane/EtOAc 4:1) gave the corresponding hemiacetal **18** (298 mg, 78%) as a light yellow oil. To a solution of **18** (223 mg, 0.36 mmol) in CH_2Cl_2 (30 mL) at first BF_3·Et_2O (100 μL, 0.79 mmol) and 5 min later thiophenol (340 μL, 3.33 mmol) were added, both at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×10 mL), and the combined organic layers were dried and filtered. After evaporation of the solvent, the residue was purified by flash chomatography (pentane/EtOAc 3:2) to afford **19** (164 mg, 76%) as a white solid. R_f=0.30 (pentane/EtOAc 3:2); m.p. 116 °C; $[\alpha]_D^{25}=-18.1$ (c=0.80 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.82 (t, J=7.6 Hz, 3H), 0.89–0.95 (m, 6H), 1.21–1.24 (m, 1H), 1.29 (d, J=6.8 Hz, 3H), 1.30–1.62 (m, 10H), 1.66–1.71 (m, 2H), 1.93–1.97 (m, 2H), 2.25–2.30 (m, 2H), 2.70–2.77 (m, 3H), 3.72–3.73 (m, 4H), 3.82–3.84 (m, 2H), 4.01–4.02 (m, 1H), 4.72–4.74 (m, 1H), 4.88 (dd, J=1.6 Hz, J= 11.1 Hz, 1H), 7.36–7.46 ppm (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ= 11.49 (q), 11.62 (q), 13.19 (q), 14.05 (q), 17.68 (t), 18.89 (t), 22.13 (t), 29.42 (t), 31.03 (t), 31.05 (t), 37.45 (d), 39.36 (t), 41.47 (t), 45.41 (d), 51.63 (q), 55.06 (d), 64.99 (d), 68.69 (d), 76.02 (d), 79.18 (d), 82.21 (d), 84.82 (d), 100.43 (s), 129.70 (d), 130.21 (d), 131.88 (s), 136.43 (d), 173.69 ppm (s); IR (KBr): ν=3530 (broad), 2960, 2927, 2871, 1726, 1446, 1429, 1380, 1365, 1350, 1304, 1281, 1262, 1246, 1175, 1136, 1096, 1072, 1040, 1020, 964, 929, 904, 885, 853, 830, 805, 760, 732, 708, 697, 667 cm^{-1}; MS (ESI):

m/z: 616.2 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{30}H_{46}O_8S_2$: C 60.17, H 7.74, S 10.71; found: C 60.28, H 8.05, S 10.54.

Azide 20: To a solution of **19** (164 mg, 274 μmol) in toluene (2 mL) Ph_3P (86 mg, 329 μmol) and HN_3 (1.43 M in toluene, 249 μL, 356 μmol) were added, and the mixture was cooled to 0 °C. At this temperature DIAD (63 μL, 329 μmol) was added dropwise. After stirring for 1 h at room temperature, the reaction was quenched with water (1 mL), and the separated aqueous layer was extracted with Et_2O (3×2 mL). The combined organic layers were dried and filtered, and the solvent was removed. Final purification of the crude product was achieved by flash chromatography (pentane/EtOAc 2:1) to give **20** (167 mg, 98%) as a white solid. R_f=0.62 (pentane/EtOAc 2:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.83 (t, J=7.6 Hz, 3H), 0.92 (t, J=7.2 Hz, 3H), 0.94 (t, J=7.4 Hz, 3H), 1.18–1.28 (m, 2H), 1.30 (d, J=6.9 Hz, 3H), 1.38–1.64 (m, 9H), 1.67–1.69 (m, 1H), 1.78–1.84 (m, 1H), 1.92–2.00 (m, 2H), 2.26–2.30 (m, 1H), 2.70–2.78 (m, 3H), 3.39–3.41 (m, 1H), 3.73–3.77 (m, 4H), 3.82 (m, 1H), 3.86–3.89 (m, 1H), 4.71–4.76 (m, 1H), 4.88 (dd, J=11.1 Hz, J=1.5 Hz, 1H), 7.35–7.46 ppm (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=11.61 (2 × q), 13.38 (q), 13.76 (q), 17.58 (t), 19.20 (t), 22.12 (t), 29.02 (t), 31.04 (t), 31.29 (t), 35.90 (t), 37.44 (d), 40.08 (t), 45.57 (d), 51.58 (q), 55.06 (d), 60.13 (d), 64.90 (d), 75.38 (d), 79.07 (d), 82.19 (d), 84.82 (d), 100.49 (s), 129.67 (d), 130.18 (d), 131.92 (s), 136.42 (d), 173.71 ppm (s); IR (KBr): ν=2939, 2878, 2098, 1736, 1460, 1442, 1371, 1353, 1310, 1275, 1264, 1229, 1204, 1169, 1130, 1077, 1024, 993, 966, 896, 842, 798, 755, 731, 704, 625 cm^{-1}; MS (ESI): *m/z*: 641.1 $[M+NH_4]^+$; elemental analysis calcd (%) for $C_{30}H_{45}N_3O_7S_2$: C 57.76, H 7.27, N 6.74, S 10.28; found: C 57.82, H 7.48, N 6.89, S 10.13.

Silyl ether 22: To a Raney Ni suspension [freshly prepared from Al/Ni alloy (5.50 g) and NaOH (7.17 g, 179 mmol)] in EtOH (80 mL) azide **20** (198 mg, 317 μmol) dissolved in a small amount of EtOH was added. The mixture was stirred for 24 h under H_2 (50 bar) at room temperature. Thereafter aqueous formalin solution (37%, 1.5 mL) was added, and the mixture was stirred for additional 24 h under H_2 (50 bar). Subsequently, the suspension was filtered over a frit, and the filtration residue was washed with EtOH (20 mL) and EtOAc/Et_3N 20:1 (3×20 mL). The solvent was removed, and the crude product was purified by flash chromatography (pentane/EtOAc/Et_3N 2:8:0.5). The resulting hydroxy ester **21** was isolated together with a small amount of N-dimethylated but not desulfurized byproduct. This mixture (81 mg) was dissolved in CH_2Cl_2 (6 mL), and then 2,6-lutidine (62 μL, 532 μmol) and TBSOTf (122 μL, 530 μmol) were added at 0 °C. After stirring for 2 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ solution (5 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3× 5 mL), and the combined organic layers were dried, filtered and evaporated. Final purification by flash chromatography (pentane/EtOAc/Et_3N 8:2:0.5) gave **22** (85 mg, 47% from **20**) as a colorless oil. R_f=0.42 (pentane/EtOAc/Et_3N 8:2:0.5); $[\alpha]_D^{25}=-0.5$ (c=0.61 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.00 (s, 3H), 0.01 (s, 3H), 0.83–0.92 (m, 21H), 1.97–1.03 (m, 1H), 1.23–1.69 (m, 15H), 1.88–1.95 (m, 4H), 2.20 (s, 6H), 2.28–2.30 (m, 1H), 2.54–2.59 (m, 1H), 3.52–3.53 (m, 1H), 3.66 (s, 3H), 3.67–3.72 (m, 1H), 3.80–3.86 (m, 2H), 4.03–4.05 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=−4.77 (q), −4.70 (q), 10.61 (q), 11.95 (q), 14.16 (q), 14.30 (q), 18.42 (s), 18.88 (t), 20.15 (t), 22.17 (t), 26.19 (q), 29.11 (t), 29.48 (t), 29.84 (t), 31.61 (t), 32.43 (t), 35.08 (t), 40.23 (q), 43.42 (d), 47.89 (d), 51.28 (q), 53.51 (d), 60.52 (d), 73.08 (d), 75.64 (d), 79.19 (d), 79.53 (d), 80.18 (d), 174.77 ppm (s); IR (neat): ν=2956, 2929, 2856, 2773, 1740, 1461, 1434, 1382, 1360, 1251, 1195, 1162, 1050, 1006, 964, 888, 835, 811, 773, 678 cm^{-1}; MS (ESI): *m/z*: 570.4 $[M+H]^+$; elemental analysis calcd (%) for $C_{32}H_{63}NO_5Si$: C 67.44, H 11.14, N 2.46; found: C 67.55, H 10.88, N 2.47.

Acid 2: To a solution of **22** (45 mg, 79 μmol) in THF/MeOH 4:1 (4 mL) 1 N LiOH (2 mL) was added. After stirring for 12 h at room temperature, the mixture was acidified with 2 N HCl (pH 5). The separated aqueous layer was then extracted with CH_2Cl_2 (3×), and the combined organic layers were dried and filtered. After evaporation, the crude poduct was purified by flash chromatography (CH_2Cl_2/MeOH 8:2) to give **2** (18 mg, 41%) as a light yellow oil. Methyl ester **22** (21 mg, 47%) was also isolated. **2**: R_f=0.28 (CH_2Cl_2/MeOH 8:2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.02 (s, 3H), 0.06 (s, 3H), 0.74 (d, J=6.9 Hz, 3H), 0.78–0.86 (m, 9H), 0.91–0.95 (m, 9H), 1.05–1.14 (m, 1H), 1.27–1.39 (m, 3H), 1.40–1.50 (m, 4H), 1.50–1.70 (m, 7H), 1.75–1.84 (m, 2H), 1.90–2.03 (m, 3H), 2.10–2.15 (m, 1H), 2.48 (s, 6H), 3.13–3.14 (m, 1H), 3.65–3.69 (m, 1H), 3.71–3.79 (m, 1H), 3.81–3.84 (m, 1H), 4.12–4.15 (m, 1H), 4.20–4.22 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=−4.84 (q), −3.21 (q), 10.07 (q), 12.29 (q), 13.86 (q), 14.33 (q), 18.64 (s), 18.74 (t), 21.27 (t), 22.74 (t), 26.37 (q), 28.29 (t), 30.67 (t), 30.74 (t), 31.39 (t), 31.90 (t), 37.92 (t), 39.22 (q), 41.74 (d), 47.36 (d), 55.63 (d), 61.38 (d), 73.20 (d), 75.29 (d), 77.18 (d), 79.67 (d), 80.51 (d), 178.32 ppm (s); MS (ESI): *m/z*: 556.4 $[M+H]^+$.

Silyl ether 23: Acid **2** (12 mg, 21.6 μmol) was dissolved in THF (0.5 mL). To this solution first Et_3N (5.3 μL, 37.8 μmol) and 10 min later 2,4,6-trichlorobenzoyl chloride (3.8 μL, 23.8 μmol) were added. The mixture was allowed to stir for 2 h at room temperature. Subsequently, the solvent was removed, and the residue was taken up in toluene (0.5 mL). This suspension was added to a solution of **4** (19 mg, 56.9 μmol) and DMAP (13.2 mg, 108 μmol) in toluene (0.5 mL). After rinsing with toluene (3× 0.3 mL), the reaction mixture was stirred for 24 h at reflux. The solvent was removed, and the crude product was purified by flash chromatography (pentane/EtOAc/Et_3N 8:2:0.5) to afford **23** (15 mg, 80%) as a light yellow oil. R_f=0.51 (pentane/EtOAc/Et_3N 8:2:0.5); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.00 (s, 3H), 0.02 (s, 3H), 0.85–0.93 (m, 24H), 0.95 (d, J=6.8 Hz, 3H), 1.10 (d, J=7.0 Hz, 3H), 1.18–1.21 (m, 1H), 1.24–1.72 (m, 21H), 1.82–1.98 (m, 7H), 2.20 (s, 6H), 2.26–2.30 (m, 1H), 2.55–2.58 (m, 2H), 3.49–3.51 (m, 1H), 3.56–3.57 (m, 1H), 3.64–3.74 (m, 2H), 3.86–3.88 (m, 1H), 3.98–4.01 (m, 1H), 4.08 (d, J=5.7 Hz, 1H), 4.88–4.90 (m, 1H), 5.12 (s, 2H), 7.28–7.35 ppm (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=−4.83 (q), −4.45 (q), 9.93 (q), 11.50 (q), 11.97 (q), 13.20 (q), 14.04 (q), 14.08 (q), 14.30 (q), 18.27 (s), 18.95 (t), 20.19 (t), 22.14 (t), 26.04 (q), 28.46 (t), 28.97 (t), 29.39 (t), 29.60 (t), 29.69 (t), 31.39 (t), 31.62 (t), 32.19 (t), 35.03 (t), 40.21 (q), 41.56 (d), 44.93 (d), 45.21 (d), 47.62 (d), 53.74 (d), 60.46 (d), 65.99 (t), 72.33 (d), 75.56 (d), 75.86 (d), 79.36 (d), 80.12 (d), 80.47 (d), 80.63 (d), 80.78 (d), 127.91 (d), 127.96 (d), 128.44 (d), 136.20 (s), 174.28 (s), 174.72 ppm (s); MS (ESI): *m/z*: 872.6 $[M+H]^+$.

Hydroxy ester 24: A solution of **23** (34 mg, 39.0 μmol) in MeCN/aqueous HF (40%) 95:5 (0.91 mL) was stirred for 5 h at room temperature. Subsequently water (3.5 mL) was added. The separated aqueous layer was extracted with CH_2Cl_2 (3×5 mL), and the combined organic layers were dried, filtered, and evaporated. Purification of the residue by flash chromatography (pentane/EtOAc/Et_3N 2:8:0.5) gave **24** (27 mg, 91%) as a light yellow oil. R_f=0.40 (pentane/EtOAc/Et_3N 2:8:0.5); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.75 (d, J=6.9 Hz, 3H), 0.84–0.91 (m, 12H), 0.94 (t, J=7.6 Hz, 3H), 1.10 (d, J=7.0 Hz, 3H), 1.18–1.38 (m, 6H), 1.39–1.60 (m, 11H), 1.64–2.01 (m, 12H), 2.18 (s, 6H), 2.30–2.35 (m, 1H), 2.47–2.49 (m, 1H), 2.55–2.58 (m, 1H), 3.64–3.67 (m, 1H), 3.82–3.85 (m, 2H), 3.88–3.91 (m, 1H), 3.96–4.03 (m, 2H), 4.06–4.09 (m, 1H), 4.86–4.89 (m, 1H), 5.12 (s, 2H), 7.28–7.34 ppm (m, 5H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=10.01 (q), 11.76 (q), 11.91 (q), 13.10 (q), 13.23 (q), 14.04 (q), 14.29 (q), 18.01 (t), 18.93 (t), 20.21 (t), 22.21 (t), 27.85 (t), 28.47 (t), 28.88 (t), 29.18 (t), 29.39 (t), 31.45 (t), 31.54 (t), 31.79 (t), 35.34 (t), 38.84 (d), 40.20 (q), 41.49 (d), 45.21 (d), 45.34 (d), 53.43 (d), 60.80 (d), 66.00 (t), 72.46 (d), 76.03 (d), 77.26 (d), 79.80 (d), 80.09 (d), 80.22 (d), 80.47 (d), 80.78 (d), 127.91 (d), 127.97 (d), 128.45 (d), 136.19 (s), 174.37 (s), 174.75 ppm (s); MS (ESI): *m/z*: 758.5 $[M+H]^+$.

Pamamycin-649 B (1 f): To a solution of **24** (10 mg, 13.2 μmol) in THF (1 mL) Pd/C (10%, 2 mg) was added. The resulting suspension was stirred for 12 h under H_2 at room temperature. After removal of the solvent and following flash chromatography (CH_2Cl_2/MeOH 9:1), *seco* acid **25** was isolated as a mixture with byproducts. It was dissolved in CH_2Cl_2 (20 mL). First, molecular sieves 4 Å (300 mg) and DMAP (11.0 mg, 90.0 μmol) were added. Then, after stirring for 30 min at room temperature, 2,4,6-trichlorobenzoyl chloride (5.6 μL, 36 μmol) was added. The reaction mixture was allowed to stir for further 48 h. Subsequently, the molecular sieves were filtered off, and the filtrate was evaporated. Finally, the residue was purified by flash chromatography (pentane/EtOAc/Et_3N 8:2:0.5) to afford pamamycin-649B (**1 f**) (4.5 mg, 53% from **24**) as a light yellow oil. R_f=0.35 (pentane/EtOAc/Et_3N 8:2:0.5); $[\alpha]_D^{25}=+12.1$ (c= 0.165 in CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.85–0.95 (m, 18H),

1.07 (d, $J=6.9$ Hz, 3H), 1.21–1.48 (m, 11H), 1.51–1.68 (m, 7H), 1.71–1.83 (m, 6H), 1.85–1.96 (m, 4H), 2.14–2.19 (m, 1H), 2.25 (s, 6H), 2.53–2.55 (m, 2H), 3.71–3.72 (m, 1H), 3.79–3.85 (m, 2H), 3.94 (m, 1H), 4.03 (m, 1H), 4.13 (m, 1H), 4.71–4.73 (m, 1H), 4.87–4.89 ppm (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): $\delta=8.42$ (q), 9.69 (q), 11.73 (q), 11.86 (q), 13.78 (q), 14.25 (q), 14.28 (q), 17.29 (t), 19.94 (t), 20.16 (t), 22.68 (t), 27.49 (t), 27.90 (t), 28.22 (t), 28.94 (t), 30.15 (t), 31.52 (t), 31.66 (t), 33.48 (t), 35.36 (t), 37.65 (d), 40.22 (q), 41.26 (d), 41.88 (d), 46.62 (d), 55.05 (d), 61.14 (d), 75.79 (d, 76.43 (d), 76.59 (d), 77.96 (d), 78.50 (d), 80.40 (d), 80.73 (d), 172.65 (s), 173.62 ppm (s); IR (neat): $\nu=2961$, 2930, 2874, 2811, 2778, 1736, 1458, 1378, 1325, 1269, 1236, 1194, 1180, 1139, 1113, 1074, 1013, 974, 947, 902, 871, 802 cm^{-1}; MS (ESI): m/z: 650.5 $[M+H]^+$; HRMS (EI positive, 70 eV) m/z calcd. for $C_{38}H_{67}NO_7$: 649.4918 $[M]^+$; found: 649.4933.

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