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Wittig cyclization of ω-hydroxy hemiacetals: Synthesis of (+)-aspicilin

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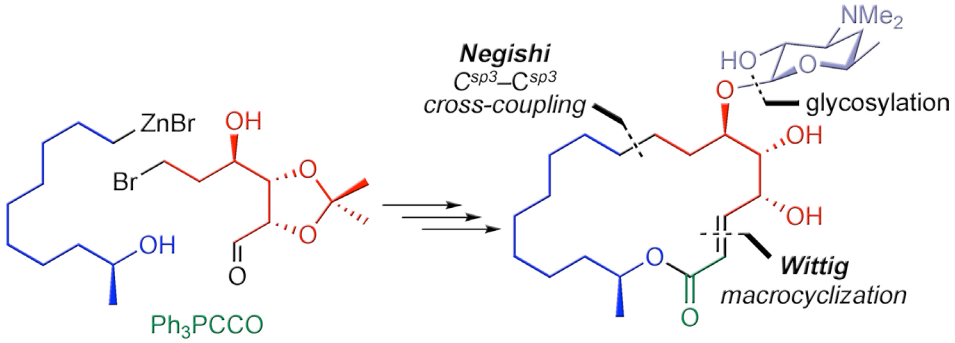


The polyhydroxylated 18-membered lichen macrolide (+)-aspicilin was synthesized in 12 steps and 17% yield (longest linear sequence) starting from D-mannose and (*S*)-propylene oxide as the source of the stereogenic centers. Key steps were a palladium-catalyzed $C^{sp^3}X–C^{sp^3}ZnX$ Negishi cross-coupling affording an ω-hydroxy hemiacetal which was macrocyclized *via* a domino addition–Wittig olefination reaction with the cumulated ylide Ph_3PCCO. This synthetic approach also allowed a regioselective glycosylation of 6-OH of aspicilin with D-desosamine, a quick entry to chimeric macrolides with potential antibiotic activity.

Introduction

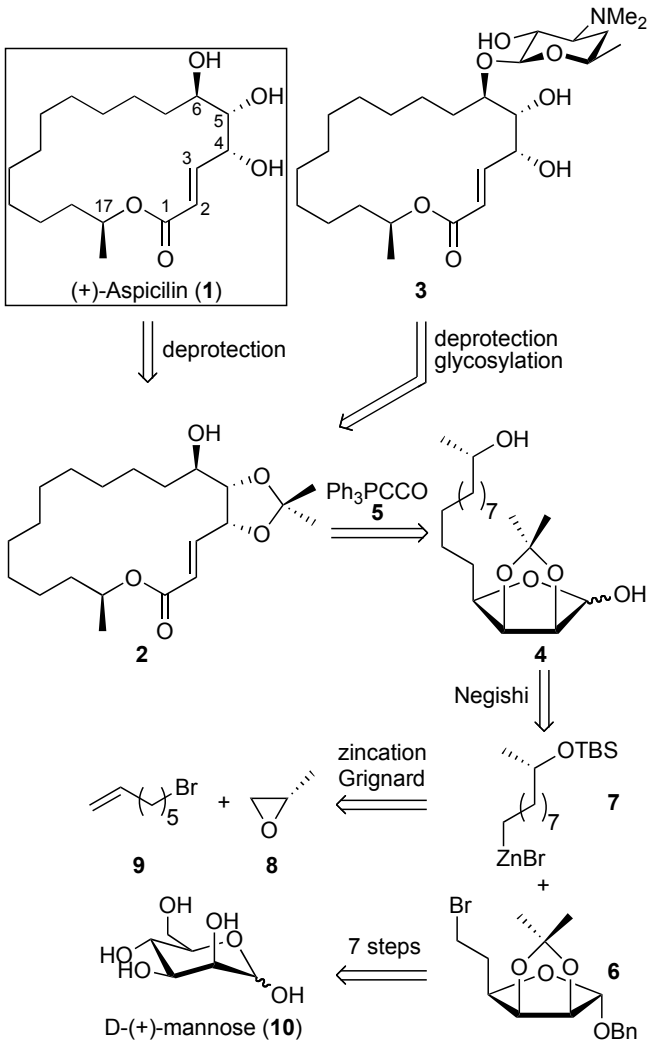
Previously, we reported the synthesis of the macrolide (+)-choriolide by a ring-closing Wittig olefination of a phosphorus ester ylide bearing an ω-hemiacetal, generated *in situ* by treating the corresponding phosphonium salt with aqueous base.[1] Though high-yielding, we intended to shorten this sequence by preparing the reactive ω-hemiacetal ester ylide directly from the corresponding ω-hydroxy hemiacetal. The 18-membered macrolactone (+)-aspicilin (**1**), first isolated in 1900 by Hesse[2] from lichen of the *lecanoraceae* family and structurally elucidated in 1973 by Huneck *et al*.,[3] is an ideal target molecule to try out this approach. It features a ring of accessible size, an *E*-configured α,β-unsaturated lactone as obtained from Wittig reactions with stabilized ylides, and a contiguous triol potentially competing for the intended glycosylation. The absolute configuration (2*E*,4*R*,5*S*,6*R*,17*S*) of **1** was established in 1985 by Quinkert *et al*.[4] by spectroscopic methods, single crystal X-ray analysis, degradation and synthetic studies. The first total synthesis of **1** was described in 1987 by Zwanenburg *et al*.[5] applying a photolactonisation of diastereomeric *o*-quinol acetates as the key step. Many more syntheses of **1** by other groups followed, differing mainly in the construction of the triol triad and the cyclization method. In most cases macrocyclization was accomplished by RCM[6] or Yamaguchi esterification.[7] Quinkert *et al*. also contributed a photochemical synthesis of **1**[8] and Oppolzer *et al*. achieved the macrocyclization by an intramolecular alkenylzinc/aldehyde addition.[9] To the best of our knowledge, the only Wittig-type macrocyclization leading to **1** was reported by Raghavan and Sreekanth[10] using an intramolecular Horner-Wadsworth-Emmons reaction under Masamune-Roush conditions which required a separate preparation of a phosphonate ester and an oxidation of an ω-alcohol to the corresponding aldehyde. Biological properties of **1** were also reported. Reddy *et al*.[7f] evaluated its antiproliferative effect against various cancer cell lines in 2012 by means of MTT assays and found activities with IC_{50} (24 h) concentrations in the low double-digit micromolar range. (+)-Aspicilin (**1**) exhibited neither antibacterial nor antifungal effects, probably due to its lack of a glycoside required for effective binding to the 50S subunit of the bacterial peptidyl tranferase.[11] In our

new synthetic approach to (+)-aspicilin (**1**) we sought to make allowance for the regioselective introduction of sugar residues such as desosamine[12] at positions 4-O, 5-O, or 6-O, in order to open access to potentially antimicrobial chimeric macrolides.

Results and Discussion

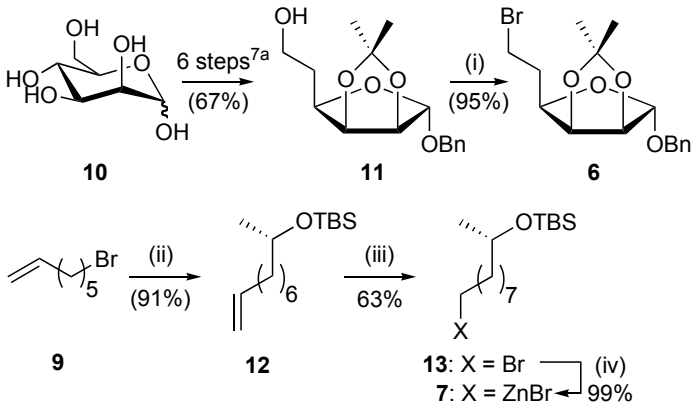
The retrosynthesis of (+)-aspicilin (**1**) is outlined in Scheme 1. It is accessible by hydrolysis of the known 4,5-acetonide protected derivative **2**[7a] which, when glycosylated with D-desosamine prior to hydrolysis, should optionally afford the 6-*O*-glycoconjugate **3**. As a key step of the synthesis, the macrocycle of **2** was to be closed by a domino addition–Wittig olefination reaction between the new acetonide protected ω-hydroxy hemiacetal **4** and the cumulated phosphorus ylide Ph_3PCCO (**5**).[13] The latter does not enter directly into Wittig olefination reactions but adds OH-, NH-, SH-, and CH-acidic compounds to give the corresponding stabilized phosphorus ylides which then undergo alkenation reactions with aldehydes and ketones.[14] Building block **4** was to be obtained by a Pd-PEPPSI™-IPr[15] catalyzed Negishi cross-coupling of a new functionalized 2,3-acetonide protected (+)-D-mannose derivative **6** with an organozinc reagent **7**. The latter introduces the required spacer and the secondary alcohol function masked as a TBS ether. It should be available by a cuprate catalyzed Grignard reaction of (*S*)-propylene oxide (**8**) and commercially available 7-bromo-1-heptene (**9**), followed by silyl protection,[7e] bromination[16] of the olefin moiety and subsequent oxidative addition of zinc.[17] Sugar bromide **6** was to be prepared from D-(+)-mannose (**10**) *via* the corresponding alcohol **11** which had already been prepared by Quinkert *et al*.[7a]

SCHEME 1. Retrosynthesis of (+)-Aspicilin (1) and its Desosamine Glycoconjugate 3



D-(+)-Mannose (**10**) was converted in six steps to alcohol **11**, according to Quinkert's protocol.[7a] Alcohol **11** was then brominated with NBS and PPh_3 to afford bromide **6** in excellent yield (Scheme 2, top). For the synthesis of organozinc reagent **7**, 7-bromo-1-heptene (**9**) was converted to its Grignard derivative which was activated with CuCN and reacted with (*S*)-propylene oxide (**8**) to give the corresponding alcohol,[7e] which was silylated right away to afford TBS ether **12** (Scheme 2, bottom). Its hydroboration with BH_3·THF and addition of bromine and NaOMe furnished bromide **13** in 63% yield.[16] While bromide **13** had been prepared before,[7a] our sequence is distinctly shorter and allows for its multi-gram scale preparation. Its reaction with zinc and catalytic amounts of iodine in 1,3-dimethyl-2-imidazolidinone (DMI) at 80 °C in a sealed Carius tube, according to a modification of the method by Huo,[17] gave organozinc compound **7** in quantitative yield (GC).

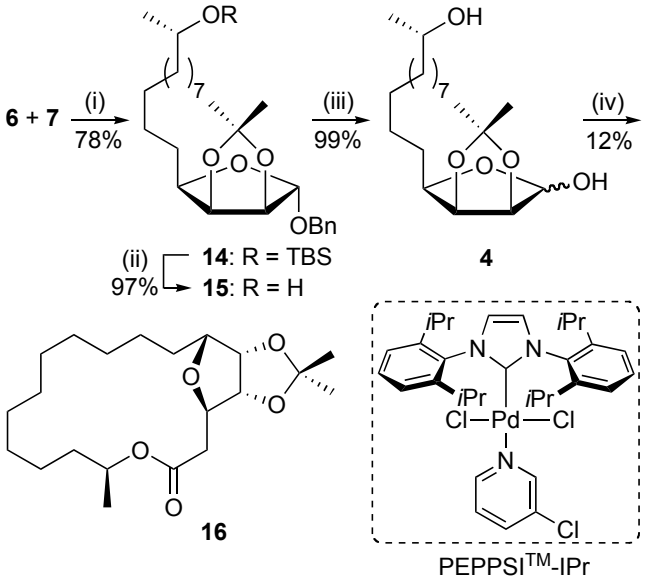
SCHEME 2.[a] **Syntheses of Bromide 6 and Organozinc Reagent 7**



[a] Reagents and conditions: (i) NBS, PPh_3, CH_2Cl_2, 0 °C to rt, 15 h; (ii) (a) Mg^0, THF, rt, 1 h, then cat. CuCN, (*S*)-propylene oxide (**8**), –78 °C to rt, 1 h; (b) TBSCl, imidazole, CH_2Cl_2, rt, 15 h; (iii) BH_3·THF, THF, 0 °C, 2 h, then Br_2, NaOMe, 40 °C, 10 min; (iv) Zn^0, cat. I_2, DMI, sealed tube, 80 °C, 18 h.

DMI was chosen because a 2:1 mixture of THF and DMI was required for the subsequent $C^{sp3}X$–$C^{sp3}ZnX$ cross-coupling of **6** and **7** using the PEPPSI™-IPr catalyst[15a] which proceeded in 78% yield to afford the known, fully protected cyclization precursor **14** in a more efficient and convenient way when compared to the literature route[7a] (Scheme 3). Other solvent mixtures gave unsatisfactory yields or no coupling reaction at all. Likewise, the use of stoichiometric amounts of LiBr was of the essence, in line with the literature.[15a] Desilylation of the cross-coupling product **14** with HF·pyridine instead of TBAF, as used in the literature,[7a] gave alcohol **15** in an immediately pure form. Catalytic debenzylation of **15** afforded the new ω-hydroxy hemiacetal **4** in an α:β ratio of 3:1 as to NMR. Its cyclization with Ph_3PCCO (**5**) required some experimentation. When refluxed in toluene for 26 h, a stoichiometric mixture of compounds **4** and **5** gave none of the desired aspicilin acetonide (**2**) but merely decomposition products and an unexpected tricyclic product **16** in low yield. The latter originated from an intramolecular Michael addition of 6-OH across the enoate of intermediate macrolactone **2**. Apparently, macrocyclization had taken place, yet under conditions that favor follow-up reactions and decomposition.

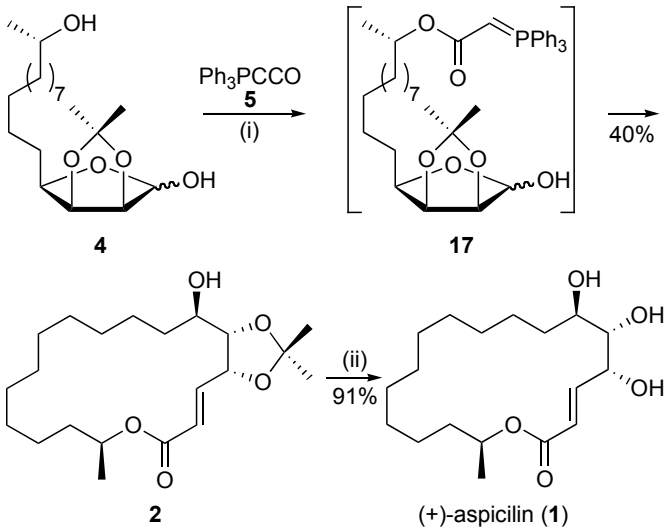
SCHEME 3.[a] **$C^{sp3}X–C^{sp3}ZnX$ Coupling and Unexpected Domino Wittig-Michael Cyclization**



[a] Reagents and conditions: (i) PEPPSI™-IPr, LiBr, THF/DMI 2:1, rt, 2 h; (ii) HF·pyridine, THF, rt, 1.5 h; (iii) H_2 (atmospheric pressure), Pd/C (10 wt%), EtOAc, rt, 2 h; (iv) Ph_3PCCO (**5**), toluene, reflux, 26 h.

However, when carried out at a lower temperature of 70 °C for a shorter period of 12 h in a sealed Carius tube, the reaction between compounds **4** and **5** afforded 40% of aspicilin acetonide (**2**) void of tricyclic **16**. These conditions seem to allow the formation of the intermediate ester ylide **17** and of its Wittig product **2** while being insufficient for the furan ring formation (Scheme 4). The natural product (+)-aspicilin (**1**) was eventually obtained in good yield as colorless crystalline platelets upon treating acetonide **2** with TFA in a mixture of MeOH and H_2O at 70 °C. Our synthetic (+)-aspicilin (**1**) showed spectroscopic properties in keeping with those reported in the literature and it was diastereopure according to NMR and GC.[4-10]

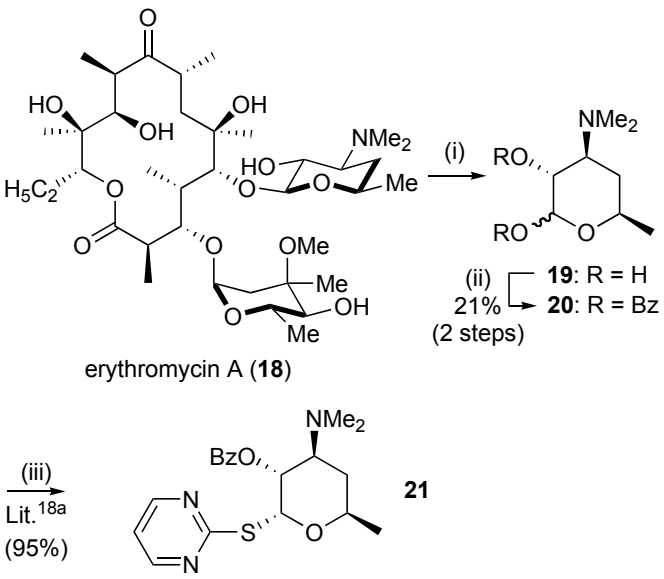
SCHEME 4.[a] **Wittig Macrocylization Leading to (+)-Aspicilin (1)**



[a] Reagents and conditions: (i) toluene, 70 °C, sealed tube, 12 h; (ii) TFA, MeOH/H_2O 3:1, 70 °C, 2 h.

For the glycosylation of alcohol **2** with D-desosamine (**19**) according to a general protocol by Woodward,[12c] the known thioglycoside **21** was prepared in three steps from commercially available erythromycin (**18**) (Scheme 5). The usual acidic hydrolysis[18] of the latter affords free D-desosamine (**19**) which is difficult to extract and purify, though. The known chemical syntheses of **19** are no option, either, to get access to larger amounts of the pure amino sugar since they are laborious or based on costly reagents and starting materials.[19] To improve the yield of D-desosamine (**19**), obtained by acidic hydrolysis of the cheap antibiotic **18**, we treated the crude hydrolysis product with Bz_2O to get the 1,2-dibenzoate **20** in an α:β ratio of 1:1.2 which was easy to extract and purify by chromatography. This was then converted to thioglycoside **21** by reaction with 2-mercaptopyrimidine under Lewis acidic conditions, according to a protocol by Zhang *et al*.[19a]

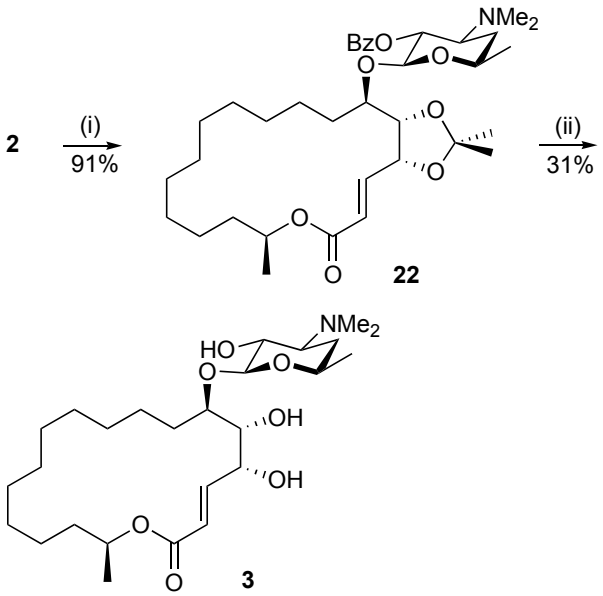
SCHEME 5.[a] **Improved Synthesis of Thioglycoside 21 from Erythromycin (18)**



[a] Reagents and conditions: (i) 6 N HCl, EtOH, reflux, 4 h; (ii) Bz_2O, NEt_3, EtOAc, rt, 22 h; (iii) 2-mercaptopyrimidine, $BF_3{\cdot}Et_2O$, dry Celite, 1,2-dichloroethane, 60 °C, 24 h.

The glycosylation of acetonide protected (+)-aspicilin **2** with thioglycoside **21** in the presence of AgOTf, following a slightly modified Woodward protocol,[12a] gave the protected derivative **22** in over 90% yield (Scheme 6). Its deprotection turned out to be rather tricky. The desired product **3** could be obtained only by first treating a solution of **22** in MeOH and H_2O with TFA at 70 °C to cleave the acetonide moiety and subsequently saponificating the benzoate with K_2CO_3 in MeOH. Saponification with aqueous base led to rapid lactone ring opening while benzoyl deprotection proceeded sluggishly. Glycoconjugate **3** is currently being tested for antimicrobial and other biological activities.

SCHEME 6.[a] **6-*O*-Glycosylation of (+)-Aspicilin (1)**



[a] Reagents and conditions: (i) AgOTf, **21**, 4 Å molecular sieves, CH_2Cl_2/toluene 2:1, rt, exclusion of light, 16 h; (ii) TFA, MeOH/H_2O 2:1, 70 °C, 2 h, then K_2CO_3, MeOH, rt, 20 h.

Conclusions

The 18-membered lichen macrolide (+)-aspicilin (**1**) was synthesized in 12 steps and 17% overall yield starting from D-mannose (**10**), 7-bromo-1-heptene (**9**) and (*S*)-propylene oxide (**8**). This synthesis comprises two unprecedented key steps, a Pd-catalyzed $C^{sp3}X–C^{sp3}ZnX$ Negishi cross-coupling with high functional group tolerance, and a one-pot Wittig-type macrocyclization of an ω-hydroxy hemiacetal with the cumulated phosphorus ylide Ph_3PCCO (**5**) as the coupling reagent. It also introduces a strategy for the regioselective attachment of D-desosamine (**19**), crucial for macrolide activity, at specific positions on the aglycone.

Experimental Section

General Remarks. Melting points were determined with a Büchi M-565 melting point apparatus and are uncorrected. IR spectra were recorded with an FT-IR spectrophotometer equipped with an ATR unit. Chemical shifts of NMR signals are given in parts per million (δ) using the residual solvent peak as an

internal standard[20], i.e., 7.26 ppm (proton) and 77.16 ppm (carbon) for $CDCl_3$. Mass spectra were obtained under EI (70 eV) conditions. High resolution mass spectra were obtained with a UPLC/Orbitrap MS system in ESI mode. GC-MS analyses were carried out on an Agilent 7890A GC system equipped with aHP-5MS column (30 m × 0.32 mm x 0.25 μm) and a 5975C inert MSD detector. Optical rotations were measured at 589 nm (Na-D line) using solutions in chloroform.

Chemicals: All reagents were purchased from commercial sources and were used without further purification. Alcohol **11**[7a] and thioglycoside **21**[19a] were prepared according to literature. All anhydrous solvents were used as supplied, except tetrahydrofuran and diethyl ether which were freshly distilled over sodium-potassium alloy, and toluene, dimethyl formamide (DMF) and 1,3-dimethyl-2-imidazolidinone (DMI) which were dried over molecular sieve (3 Å).[21] Moisture or air sensitive reactions were routinely carried out in oven-dried glassware under an argon atmosphere using standard Schlenk technique.

Chromatography: Analytical thin layer chromatography was carried out using Merck silica gel 60GF254 pre-coated aluminium-backed plates and/or Merck 60 RP-18 F254S foil plates. Column chromatography was performed at medium pressure using dry packed Marchery-Nagel silica gel 60, pore size 40–63 μm with the eluent specified. Flash vacuum chromatography was performed using dry packed Marchery-Nagel silica gel 60, pore size 25–40 μm with the eluent specified.

(+)-Aspicilin (1). According to literature[7a] macrolide **2** (10 mg, 0.027 mmol) was dissolved in a mixture of methanol (3 mL) and H_2O (1 mL), treated with TFA (0.1 mL, 1.38 mmol) and warmed under stirring at 70 °C. After complete deprotection (TLC, 2 h) the reaction was quenched with sat. aqueous $NaHCO_3$ (10 mL) and brine (10 mL), and extracted three times with methyl *t*-butyl ether (15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. After recrystallization of the residue from a mixture of *n*-hexane and ethyl acetate (+)-aspicilin (**1**) was obtained as colorless platelets (8 mg, 0.025 mmol, 91%) of mp 151–152 °C (lit[6h] mp 150–155 °C; lit[7a] mp 154–156 °C; lit[7b] mp 150–152 °C;

lit[7d] mp 152–155 °C); R_f = 0.14 (50% ethyl acetate in *n*-hexane); $[\alpha]^{23}_D$ +37.5 (*c* 0.11, $CHCl_3$) (lit[6h] $[\alpha]^{28}_D$ +35.0 (*c* 0.20 $CHCl_3$); lit[7b] $[\alpha]^{23}_D$ +37.7 (*c* 0.22 $CHCl_3$); lit[7c] $[\alpha]^{23}_D$ +38.5 (*c* 0.22 $CHCl_3$); lit[7d] $[\alpha]^{22}_D$ +37.5 (*c* 0.55 $CHCl_3$)); IR ν_{max} 3441, 3280, 2926, 2855, 1716, 1664, 1460, 1363, 1342, 1232, 1179, 1072, 1035, 1009, 988, 951, 802, 762, 588 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.90 (dd, *J* = 15.9, 5.2 Hz, 1 H), 6.12 (dd, *J* = 15.9, 1.6 Hz, 1 H), 5.05 (dqd, *J* = 6.3, 6.0, 5.8 Hz, 1 H), 4.53–4.62 (m, 1 H), 3.72–3.82 (m, 1 H), 3.54–3.62 (m, 1 H), 3.17–3.34 (m, 1 H), 2.99–3.13 (m, 1 H), 2.40–2.55 (m, 1 H), 1.16–1.64 (m, 23 H); ^{13}C NMR ($CDCl_3$,75 MHz) δ 165.6, 144.7, 123.3, 75.0, 73.4, 71.3, 70.1, 35.9, 32.3, 28.5, 27.9, 27.8, 27.4, 27.3, 26.6, 24.4, 23.8, 20.6; HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_{18}H_{33}O_5^+$ 329.2323, found 329.2319.

(1*R*,2*E*,6*S*,17*R*,18*S*)-17-Hydroxy-6,20,20-trimethyl-5,19,21-trioxabicyclo[16.3.0]henicos-2-en-4-one (2). A stirred solution of ω-hydroxy hemiacetal **4** (198 mg, 0.58 mmol) and Ph_3PCCO (**5**) (174 mg, 0.58 mmol) in dry toluene (8 mL) was heated in a sealed Carius tube for 12 h at 70 °C. The volatiles were removed *in vacuo* and the residue was purified by column chromatography eluting with 10% ethyl acetate in *n*-hexane to afford the macrolide **2** as a colorless crystalline solid (72 mg, 0.20 mmol, 40%) of mp 112–114 °C (lit[8b] mp 114–115 °C); R_f = 0.82 (10% ethyl acetate in *n*-hexane); $[\alpha]^{23}_D$ +56.2 (*c* 0.18, $CHCl_3$) (lit[8b] $[\alpha]^{20}_D$ +56.9 (*c* 0.82 $CHCl_3$)); IR ν_{max} 3463, 2925, 2857, 1706, 1659, 1461, 1370, 1252, 1183, 1129, 1086, 1034, 992, 858, 797, 596; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.85 (dd, *J* = 15.6, 8.8 Hz, 1 H), 5.98 (d, *J* = 15.6 Hz, 1 H), 5.10 (dqd, *J* = 6.3, 6.0, 5.8 Hz, 1 H), 4.58 (dd, *J* = 8.8, 6.3 Hz, 1 H), 4.04 (dd, *J* = 8.6, 6.2 Hz, 1 H), 3.54–3.67 (m, 1 H), 2.19 (d, *J* = 1.4 Hz, 1 H), 1.19–1.59 (m, 29 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 165.4, 142.7, 124.6, 109.8, 82.3, 76.9, 71.0, 69.2, 35.7, 32.7, 28.2, 28.1, 27.7, 27.6, 27.2, 27.1, 26.2, 25.7, 24.4, 23.5, 20.6; MS (EI, 70 eV) *m/z* 368 (M^+), 353, 277, 157, 142, 114; HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{37}O_5^+$ 369.2636, found 369.2630.

(3*E*,5*R*,6*S*,7*R*,18*S*)-7-*O*-[3',4',6'-trideoxy-(dimethylamino)-β-D-xylo-hexopyranosyl]-5,6-dihydroxy-18-methyloxacyclooctadec-3-en-2-one (3). A stirred solution of protected glycosyl

macrolide **22** (12 mg, 0.02 mmol) in a mixture of methanol (500 μL) and H_2O (250 μL) was treated with TFA (75 μL, 0.99 mmol) at ambient temperature and then stirred at 70 °C for 2 h. After deprotection of the acetonide moiety (TLC) the reaction was quenched with sat. aqueous $NaHCO_3$ (3 mL) and brine (3 mL) and extracted three times with ethyl acetate (15 mL). The combined organic layers were dried ($MgSO_4$) and the volatiles were removed *in vacuo*. The residue was taken up in methanol (200 μL) and treated with freshly ground K_2CO_3 (3 mg, 21 μmol) at ambient temperature. After stirring for 20 h the reaction mixture was filtered over a plug of silica gel and washed with a mixture of acetone and 0.1% NEt_3 (20 mL). The filtrates were concentrated and purified by column chromatography eluting with acetone and 0.1% NEt_3 to give glycosyl macrolide **3** as a slightly yellowish and highly viscous oil (3 mg, 0.006 mmol, 31%); R_f = 0.28 (0.1% NEt_3 in acetone); IR ν_{max} 3395, 2926, 2854, 2218, 1727, 1272, 1164, 1067, 716, 576, 569 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.15 (dd, J = 15.6, 4.2 Hz, 1 H), 6.18 (dd, J = 15.6, 1.9 Hz, 1 H), 4.89–5.03 (m, 2 H), 4.43 (d, J = 7.1 Hz, 1 H), 4.32–4.39 (m, 1 H), 3.99–4.12 (m, 1 H), 3.85–3.96 (m, 1 H), 3.56–3.68 (m, 3 H), 3.43–3.52 (m, 1 H), 3.32–3.40 (m, 1 H), 2.90 (br. s., 6 H), 2.24–2.41 (m, 1 H), 1.47–1.80 (m, 1 H), 1.21–1.44 (m, 23 H), 1.18 (d, J = 6.0 Hz, 3 H); HRMS (+ESI) m/z $[M+H]^+$ calcd for $C_{26}H_{48}O_7N^+$ 486.3425, found 486.3418.

(10'*S*)-5-Deoxy-5-*C*-(10'-hydroxyundecyl)-2,3-*O*-isopropylidene-α-D-lyxofuranoside (4). A mixture of palladium on charcoal (10wt%, 0.2 g), benzyl ether **15** (0.89 g, 2.1 mmol) and ethyl acetate (50 mL) was hydrogenated at room temperature at 1 bar of H_2 for 2 h (TLC control). The reaction mixture was filtered over a plug of celite® 545 and the filtrate was washed with ethyl acetate (50 mL). The combined organic phases were concentrated *in vacuo* to leave ω-hydroxy hemiacetal **4** as a colorless solid (0.72 g, 2.1 mmol, 99%) of mp 62-64 °C, consisting of a 3:1 mixture of α and β anomers as to ^1H NMR. R_f = 0.15 (30% ethyl acetate in *n*-hexane); $[\alpha]^{23}_D$ +14.5 (*c* 0.67, $CHCl_3$); IR ν_{max} 3392, 2925, 2850, 1461, 1401, 1379, 1208, 1164, 1129, 1083, 1060, 1025, 1009, 973, 933, 903, 826, 737, 679 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) *mixture of anomers*: δ 5.34 (d, J = 2.2 Hz, 1 H), 4.93 (dd, J = 12.1, 3.6 Hz,

1 H), 4.65 (dd, *J* = 6.0, 3.6 Hz, 1 H), 4.54–4.62 (m, 2 H), 4.48 (dd, *J* = 6.0, 3.6 Hz, 1 H), 4.12 (td, *J* = 6.8, 3.4 Hz, 1 H), 3.73–3.87 (m, 2 H), 3.46 (ddd, *J* = 7.2, 6.3, 3.0 Hz, 1 H), 2.43 (d, *J* = 2.5 Hz, 1 H), 1.62–1.78 (m, 4 H), 1.22–1.59 (m, 32 H), 1.18 (d, *J* = 6.0 Hz, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) *mixture of anomers*: δ 101.0, 96.5, 85.9, 80.6, 80.5, 78.9, 76.1, 68.4, 41.0, 39.4, 29.8, 29.7, 29.7, 29.6, 29.6, 29.5, 29.5, 28.5, 28.3, 26.9, 26.3, 26.2, 26.1, 26.0, 25.9, 25.8, 25.4, 25.2, 25.1, 24.0, 23.6, 20.9, 17.4; HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_{19}H_{37}O_5^+$ 345.2641, found 345.2650.

Benzyl 6-bromo-5-deoxy-2,3-*O*-(1-methylethylidene)-α-D-*lyxo*-hexofuranoside (6). A solution of 5-deoxy-2,3-O-(1-methylethylidene)-α-D-lyxo-hexofuranoside (**11**)[7a] (8.52 g, 28.9 mmol) and triphenylphosphane (19.00 g, 72.3 mmol) in dry CH_2Cl_2 (300 mL) was treated with *N*-bromosuccinimide (12.89 g, 72.3 mmol) at 0 °C and the resulting mixture was stirred and allowed to warm to room temperature. After 15 h, sat. aqueous $NaHCO_3$ (100 mL) was added and the layers were separated. The aqueous one was extracted twice with CH_2Cl_2 (200 mL) and the combined organic layers were dried (anhydrous $MgSO_4$). The volatiles were removed *in vacuo* and the resulting black oil was purified by vacuum flash chromatography eluting with 10% ethyl acetate in *n*-hexane to give the title compound after recrystallization from *n*-hexane as colorless needles (9.72 g, 27.2 mmol, 95%); R_f = 0.33 (5% ethyl acetate in *n*-hexane); mp 65-66 °C; $[\alpha]^{23}_D$ +93 (*c* 1.04, $CHCl_3$); IR (neat) ν_{max} 2928, 1376, 1357, 1271, 1082, 1014, 862, 700, 652, 554 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.26–7.37 (m, 5 H), 5.07 (s, 1 H), 4.64–4.72 (m, 2 H), 4.69 (d, *J* = 11.8 Hz, 1 H), 4.49 (d, *J* = 11.8 Hz, 1 H), 4.24 (ddd, *J* = 8.1, 4.9, 2.6 Hz, 1 H), 3.57 (dt, *J* = 6.6, 1.1 Hz, 1 H), 2.34 (ddt, *J* = 14.3, 8.5, 5.8 Hz, 1 H), 2.18 (dtd, *J* = 14.2, 7.4, 4.8 Hz, 1 H), 1.45 (s, 3 H), 1.31 (s, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.5, 128.6, 128.3, 128.0, 112.6, 105.1, 85.5, 80.3, 77.8, 69.0, 31.8, 30.6, 26.2, 25.0; HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{22}BrO_4^+$ 357.0704, found 357.0701.

(*S*)-*t*-Butyl(dec-9-en-2-yloxy)dimethylsilane (12). A Grignard solution was prepared from 7-bromo-1-heptene (**9**) (19.78 g, 111.7 mmol), THF (200 mL) and magnesium turnings (2.85 g, 117.3 mmol) and

added *via* cannula to a solution of (*S*)-propylene oxide (**8**) (7.8 mL, 111.7 mmol) and copper(I) cyanide (0.50 g, 5.59 mmol) in THF (200 mL) at –78 °C. The mixture was allowed to warm to room temperature and quenched after 1 h with conc. aqueous ammonia (100 mL) and sat. aqueous NH_4Cl (100 mL). The resulting mixture was extracted three times with methyl *t*-butyl ether (300 mL) and the combined organic layers were dried (anhydrous $MgSO_4$). After removing the volatiles *in vacuo* the crude alcohol was obtained as a colorless oil. It was dissolved in dry CH_2Cl_2 (250 mL) and the resulting solution was treated with *t*-butyldimethylsilyl chloride (17.68 g, 117.3 mmol), imidazole (9.13 g, 134.0 mmol) and DMAP (1.37 g, 11.2 mmol) and the mixture was stirred at room temperature for 15 h. The volatiles were removed *in vacuo* and the residue was taken up in *n*-hexane (100 mL), sat. aqueous $NaHCO_3$ (100 mL) was added and the organic layer was separated. The aqueous layer was extracted three times with *n*-hexane (150 mL) and the combined organic layers were dried (anhydrous $MgSO_4$). After removal of the volatiles *in vacuo* the title compound was obtained without further purification as a colorless oil (27.50 g, 101.6 mmol, 91%). R_f = 0.28 (*n*-hexane); $[\alpha]^{23}_D$ +9.6 (*c* 1.10, $CHCl_3$); IR (neat) ν_{max} 2928, 2856, 1642, 1463, 1374, 1254, 1133, 1048, 993, 909, 833, 807, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.81 (ddt, *J* = 17.1, 10.4, 6.7 Hz, 1 H), 4.99 (ddt, *J* = 17.1, 1.8, 1.5 Hz, 1 H), 4.93 (ddt, *J* = 10.2, 2.1, 1.2 Hz, 1 H), 3.76 (dq, *J* = 11.7, 6.1 Hz, 1 H), 2.04 (dtt, *J* = 7.4, 7.0, 1.2 Hz, 2 H), 1.19–1.48 (m, 10 H), 1.11 (d, *J* = 6.1 Hz, 3 H), 0.88 (s, 9 H), 0.04 (d, *J* = 1.2 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 139.4, 114.3, 68.8, 39.9, 34.0, 29.7, 29.3, 29.0, 26.1, 25.9, 24.0, –4.3, –4.6; HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{35}OSi^+$ 271.2457, found 271.2461.

(*S*)-(10-Bromodecan-2-yloxy)(*t*-butyl)dimethylsilane (13). A stirred solution of (*S*)-*t*-butyl(dec-9-en-2-yloxy)dimethylsilane (**12**) (6.26 g, 23.1 mmol) in dry THF (10 mL) was treated with BH_3·THF complex (14.0 mL, 13.9 mmol, 1.0 M solution in THF) which was added by a syringe pump at 0 °C at a rate of 1mL/min. The reaction mixture was allowed to warm to room temperature. After 2 h the mixture was warmed to 40 °C and bromine (1.2 mL, 23.1 mmol) and sodium methoxide (5.8 mL, 25.4 mmol, 4.4 M in methanol) were added simultaneously, so that the mixture took on a persisting yellowish

tinge. It was quenched by adding sat. aqueous K_2CO_3, extracted three times with *n*-hexane (150 mL) and the combined organic layers were dried (anhydrous $MgSO_4$). After removal of the volatiles *in vacuo* and purifying the residue by filtration over a short plug of silica eluting with 10 % CH_2Cl_2 in *n*-hexane the title compound was obtained as a colorless oil (5.12 g, 14.6 mmol, 63%); R_f = 0.79 (5% ethyl acetate in *n*-hexane). $[\alpha]^{23}_D$ +8.7 (*c* 1.26, $CHCl_3$) (lit[7a] $[\alpha]^{20}_D$ +8.7 (*c* 1,16 $CHCl_3$)); IR (neat) ν_{max} 2928, 2856, 1463, 1374, 1253, 1131, 1056, 1005, 833, 808, 772, 724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.71–3.82 (m, 1 H), 3.40 (t, J = 6.9 Hz, 2 H), 1.85 (quin, J = 7.1 Hz, 2 H), 1.23–1.47 (m, 12 H), 1.11 (d, J = 6.0 Hz, 3 H), 0.88 (s, 9 H), 0.04 (d, J = 0.8 Hz, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 68.6, 39.7, 34.0, 32.8, 29.7, 29.6, 29.4, 28.7, 28.2, 25.9, 25.7, 23.8, –4.4, –4.7 ppm; HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_{16}H_{36}BrOSi^+$ 351.1719, found 351.1723.

(10'*S*)-Benzyl 5-*C*-{10'-[(*t*-butyl)dimethylsilyloxy]undecyl}-5-deoxy-2,3-*O*- isopropylidene-α-D-*lyxo*furanoside (14). A Carius tube was charged under an argon atmosphere with a solution of bromide **13** (2.05 g, 5.8 mmol) in dry 1,3-dimethyl-1,2-imidazolidinone (4 mL), zinc dust (1.15 g, 17.5 mmol), and iodine (46 mg, 0.18 mmol), and then sealed and heated at 80 °C for 18 h while stirring. After cooling to room temperature the reaction mixture containing organozinc compound **7** was transferred *via* cannula to a stirred solution of PEPPSI™-IPr ([1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride) (50 mg, 0.072 mmol) and freshly dried LiBr (1.01 g, 11.7 mmol) in dry THF (16 mL) and dry 1,3-dimethyl-1,2-imidazolidinone (4 mL). A slow change of color from yellowish to deep brown indicated the formation of the catalyst. Bromide **6** (1.30 g, 3.6 mmol) was added in one portion and stirring at room temperature was continued for 2 h. The reaction was quenched by addition of an 0.5 M aqueous solution of Na_3EDTA (50 mL) and extracted three times with a mixture of *n*-hexane and Et_2O (1:1, 100 mL). The organic layers were combined, dried (anhydrous $MgSO_4$), and concentrated *in vacuo*. Purification of the remainder by column chromatography with 5% methyl *t*-butyl ether in *n*-hexane afforded product **14** as a colorless viscous oil

(1.54 g, 2.8 mmol, 78%). R_f = 0.55 (50% ethyl acetate in *n*-hexane); $[\alpha]^{23}_D$ +47.9 (*c* 1.22, $CHCl_3$) (lit[7a] $[\alpha]^{20}_D$ +49.5 (*c* 1,23 $CHCl_3$)); IR ν_{max} 2927, 2856, 1463, 1372, 1255, 1209, 1085, 1016, 834, 807, 773, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.38 (m, 5 H), 5.06 (s, 1 H), 4.67 (d, *J* = 11.8 Hz, 1 H), 4.60–4.64 (m, 2 H), 4.48 (d, *J* = 11.8 Hz, 1 H), 3.96 (td, *J* = 7.0, 1.8 Hz, 1 H), 3.78 (dqd, *J* = 6.3, 6.0, 5.8 Hz, 1 H), 1.71 (ddd, *J* = 14.1, 7.2, 6.4 Hz, 2 H), 1.24–1.48 (m, 26 H), 1.12 (d, *J* = 6.0 Hz, 3 H), 0.90 (s, 9 H), 0.05 (s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.8, 128.6, 128.2, 127.9, 112.3, 105.3, 85.5, 80.6, 80.3, 69.0, 68.8, 39.9, 29.9, 29.8, 29.8, 29.7, 28.5, 26.4, 26.3, 26.1, 26.0, 25.1, 24.0, 18.3, –4.2, –4.6; HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_{32}H_{57}O_5Si^+$ 549.3975, found 549.3979.

(10'*S*)-Benzyl 5-Deoxy-5-*C*-(10'-hydroxyundecyl)-2,3-*O*-isopropylidene-α-D-lyxofuranoside (15). A solution of silyl ether **14** (1.17, 2.1 mmol) in THF (10 mL) was treated with HF·pyridine (70wt%, 2.2 mL) at ambient temperature and the resulting mixture was stirred for 1.5 h. Water (10 mL) and sat. aqueous K_2CO_3 (10 mL) were added and the mixture was extracted three times with methyl *t*-butyl ether (50 mL). The combined organic layers were washed in turn with sat. aqueous $CuSO_4$ (100 mL), H_2O (20 mL) and brine (50 mL). Drying the organic layer (anhydrous $MgSO_4$) and removing the volatiles *in vacuo* yielded product alcohol **15** as a colorless solid without further purification (0.89 g, 2.1 mmol, 97%). R_f = 0.27 (20% ethyl acetate in *n*-hexane); mp 41–42 °C (lit[7a] mp 41–41.5 °C); $[\alpha]^{23}_D$ +57.5 (*c* 1.05, $CHCl_3$) (lit[7a] $[\alpha]^{20}_D$ +59.0 (*c* 1,05 $CHCl_3$)); IR ν_{max} 2925, 2854, 1456, 1372, 1268, 1208, 1164, 1076, 1014, 873, 733, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.38 (m, 5 H), 5.05 (s, 1 H), 4.66 (d, *J* = 11.8 Hz, 1 H), 4.60–4.63 (m, 2 H), 4.48 (d, *J* = 11.8 Hz, 1 H), 3.92–4.00 (m, 1 H), 3.78 (dqd, *J* = 6.3, 6.0, 5.8 Hz, 1 H), 1.63–1.78 (m, 2 H), 1.26–1.47 (m, 26 H), 1.18 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 137.7, 128.6, 128.2, 127.9, 112.3, 105.3, 85.4, 80.6, 80.3, 68.9, 68.3, 39.5, 29.8, 29.8, 29.7, 29.7, 29.6, 28.5, 26.4, 26.3, 25.9, 25.1, 23.6; HRMS (+ESI) *m/z* $[M+Na]^+$ calcd for $C_{26}H_{42}O_5Na^+$ 457.2925, found 457.2914.

(1*R*,2*R*,6*S*,17*R*,18*S*)-6,20,20-trimethyl-5,19,21,22-tetraoxatricyclo[14,5,1,$0^{1,18}$]docosan-4-one (16).

A stirred solution of ω-hydroxy hemiacetal **4** (60 mg, 0.17 mmol) and Ph_3PCCO (**5**) (52 mg, 0.17 mmol) in dry toluene (3 mL) was heated at reflux for 26 h. The volatiles were removed *in vacuo* and the remainder was purified by column chromatography with 5% ethyl acetate in *n*-hexane to afford the furan **16** as a colorless crystalline solid (8 mg, 0.021 mmol, 12%) of mp 95–97 °C. R_f = 0.82 (10% ethyl acetate in *n*-hexane); $[\alpha]^{23}_D$ +37 (*c* 0.10, $CHCl_3$); IR ν_{max} 2926, 2855, 1723, 1461, 1378, 1271, 1234, 1208, 1165, 1068, 891, 860, 802 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.97–5.10 (m, 1 H), 4.54–4.65 (m, 2 H), 4.48 (dd, *J* = 6.2, 1.2 Hz, 1 H), 3.82 (dt, *J* = 8.9, 3.4 Hz, 1 H), 2.49 (dd, *J* = 15.1, 11.8 Hz, 1 H), 2.29 (dd, *J* = 15.1, 2.5 Hz, 1 H), 1.75–1.88 (m, 1 H), 1.57–1.66 (m, 1 H), 1.22–1.57 (m, 24 H), 1.20 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.5, 112.8, 85.4, 82.4, 80.9, 79.3, 71.6, 36.5, 36.4, 28.7, 28.1, 27.6, 27.6, 27.5, 26.8, 26.6, 26.5, 25.9, 25.6, 24.6, 20.6; MS (EI, 70 eV) *m/z* 368 (M^+), 353, 324, 293, 233, 114; HRMS (+ESI) *m/z* $[M+H]^+$ calcd for $C_{21}H_{37}O_5^+$ 369.2636, found 369.2634.

D-Desosamine-1,2-dibenzoate (20). According to the literature[18b] a stirred solution of erythromycin (**18**) (50 g, 68 mmol) in ethanol (300 mL) and 6 N HCl (800 mL) was heated to reflux for 4 h. The aqueous acidic solution was cooled to ambient temperature and decanted from a black tar. The solution was extracted 10 times with $CHCl_3$ (2 L). The aqueous layer was then decolorised with charcoal (100 g) and filtered over a plug of celite® 545. The volatiles were thoroughly removed *in vacuo* and the resulting yellowish brown slurry of crude D-desosamine hydrochloride was dissolved in ethyl acetate (250 mL) and treated with NEt_3 (19.4 mL, 140 mmol), benzoic anhydride (33.9 g, 150 mmol), and DMAP (3.7 g, 30 mmol). After stirring for 22 h, 5% aqueous $NaHCO_3$ solution (150 mL) was added. The mixture was stirred vigorously for another 30 min and then extracted three times with ethyl acetate (300 mL). The combined organic layers were dried ($MgSO_4$) and the volatiles were removed *in vacuo*. The residue was partitioned between diethyl ether (200 mL) and 0.5 N HCl (200 mL), the ether layer was separated and extracted two more times with 0.5 N HCl (200 mL). The combined acidic aqueous layers were treated with 6 N NaOH to adjust pH 8 and the resulting milky aqueous suspension was

extracted five times with CH_2Cl_2 (250 mL). The combined organic layers were dried ($MgSO_4$), the volatiles were removed *in vacuo* and the residue was purified by column chromatography with 10% acetone and 0.1% NEt_3 in *n*-hexane to afford the sugar **20** as a fawn foam (5.48 g, 14.3 mmol, 21%, 1:1.2 mixture of α and β anomers as to ^{1}H NMR).R_f = 0.51 (30% ethyl acetate in *n*-hexane) (lit[19a] R_f = 0.47 (30% ethyl acetate in *n*-hexane)); ^{1}H NMR ($CDCl_3$, 300 MHz) *α-anomer*: δ 8.05–8.12 (m, 2 H), 7.89 - 8.03 (m, 2 H), 7.57–7.65 (m, 1 H), 7.44–7.53 (m, 5 H), 6.60 (d, *J* = 3.6 Hz, 1 H), 5.39–5.49 (m, 1 H), 4.23 (dqd, *J* = 11.6, 6.0, 2.1 Hz, 1 H), 3.44 (ddd, *J* = 12.3, 11.0, 4.1 Hz, 1 H), 2.37 (s, 6 H), 1.98 (ddd, *J* = 13.4, 4.3, 2.1 Hz, 1 H), 1.63 (dd, *J* = 12.8, 9.3 Hz, 1 H), 1.27 (d, *J* = 6.3 Hz, 3 H); *β-anomer*: δ 7.89–8.03 (m, 4 H), 7.28–7.40 (m, 6 H), 5.97 (d, *J* = 8.0 Hz, 1 H), 5.39–5.49 (m, 1 H), 3.89 (dqd, *J* = 11.6, 6.0, 2.1 Hz, 1 H), 3.07 (ddd, *J* = 12.3, 10.5, 4.4 Hz, 1 H), 2.35 (s, 6 H), 1.90 (ddd, *J* = 13.4, 4.3, 2.1 Hz, 1 H), 1.55 (dd, *J* = 12.8, 9.3 Hz, 1 H), 1.34 (d, *J* = 6.0 Hz, 3 H).

(1*R*,2*E*,6*S*,17*R*,18*S*)-17-*O*-[3',4',6'-trideoxy-3'-(dimethylamino)-β-D-xylo-hexopyranosyl-2'-benzoate]-6,20,20-trimethyl-5,19,21-trioxabicyclo[16.3.0]henicos-2-en-4-one (22). According to a general protocol,[12a] a suspension of AgOTf (75 mg, 0.29 mmol) and powdered 4 Å molecular sieve (200 mg) in dry CH_2Cl_2 (4 mL) and toluene (4 mL) at 0 °C was treated with a solution of 1-(2'-pyrimidinethio)3,4,6,-trideoxy-2-*O*-benzoyl-3-(dimethylamino)-D-xylo-hexopyranoside (**21**) (91 mg, 0.24 mmol) in dry CH_2Cl_2 (2 mL) and with a solution of macrolide **2** (18 mg, 0.049 mmol) in dry CH_2Cl_2 (2 mL). The resulting reaction mixture was stirred at ambient temperature in the dark for 16 h, the molecular sieve was filtered off and sat. aqueous $NaHCO_3$ (5 mL) was added. The resulting mixture was extracted three times with ethyl acetate (30 mL), the combined organic layers were dried ($MgSO_4$), and the volatiles were removed *in vacuo*. After column chromatography with 10% acetone and 0.1% NEt_3 in *n*-hexane the desired product was obtained as a highly viscous colorless oil (28 mg, 0.046 mmol, 91%). R_f = 0.32 (20% acetone and 0.1% NEt_3 in *n*-hexane); $[\alpha]^{23}_D$ +28 (*c* 1.51, $CHCl_3$); IR ν_{max} 2929, 2858, 1718, 1452, 1369, 1268, 1249, 1164, 1123, 1105, 1056, 987, 859, 709, 638, 564 cm^{-1};

^{1}H NMR ($CHCl_3$, 300 MHz) δ 8.01–8.08 (m, 2 H), 7.47–7.53 (m, 1 H), 7.37–7.45 (m, 2 H), 6.90 (dd, J = 15.5, 8.9 Hz, 1 H), 5.92 (dd, J = 15.6, 0.8 Hz, 1 H), 5.03–5.15 (m, 2 H), 4.65 (d, J = 7.7 Hz, 1 H), 4.50 (ddd, J = 8.7, 5.8, 0.7 Hz, 1 H), 4.26 (dd, J = 8.4, 5.6 Hz, 1 H), 3.52–3.67 (m, 2 H), 2.89 (ddd, J = 12.3, 10.5, 4.4 Hz, 1 H), 2.28 (s, 6 H), 1.79 (ddd, J = 12.9, 4.4, 1.9 Hz, 1 H), 1.51 (s, 3 H), 1.37 (s, 3 H), 1.29 (d, J = 6.1 Hz, 3 H), 1.22 (d, J = 6.3 Hz, 3 H), 0.67–1.57 (m, 33 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.7, 165.5, 143.1, 132.8, 130.8, 130.0, 128.4, 124.4, 109.7, 102.6, 81.2, 79.3, 77.4, 72.2, 70.9, 69.5, 64.0, 40.9, 35.6, 31.6, 29.9, 28.4, 27.8, 27.6, 27.3, 27.1, 26.7, 26.0, 25.9, 24.6, 23.4, 21.5, 20.5; HRMS (+ESI) m/z $[M+H]^+$ calcd for $C_{36}H_{56}O_8N^+$ 630.4000, found 630.3987.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **1–4**, **6, 12-16**, **20** and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES

(1) Ostermeier, M.; Schobert, R. *J. Org. Chem.* **2014**, *79* (9), 4038-4042.

(2) (a) Hesse, O. *J. Prakt. Chem.* **1900**, *62*, 430-480. (b) Hesse, O. *J. Prakt. Chem.* **1904**, *70*, 449-502.

(3) Huneck, S; Schreiber, K.; Steglich, W. *Tetrahedron* **1973**, *29*, 3687-3693.

(4) Quinkert, G.; Heim, N.; Bats, J. W.; Oschkinat, H.; Kessler, H. *Angew. Chem.* **1985**, *97*, 985-986; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 987.

(5) Waanders, P. P.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1987**, *28*, 2409-2412.

(6) (a) Schaubach, S.; Michigami, K.; Fürstner, A. *Synthesis* **2017**, *49*, 202-208. (b) Saidhareddy, P.; Ajay, S.; Shaw, A. K. *RSC Adv.* **2014**, *4*, 4253-4259. (c) Zhang, H.; Yu, E. C.; Torker, S.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2014**, *136*, 16493-16496. (d) Wang, C.-Y.; Hou, D.-R. *J. Chin.*

Chem. Soc. **2012**, *59*, 389-393. (e) Yadav, J. S.; Rao, T. S.; Ravindar, K.; Subba Reddy, B. V. *Synlett* **2009**, *17*, 2828-2830. (f) Dixon, D. J.; Foster, A. C.; Ley, S. V. *Can. J. Chem.* **2001**, *79*, 1668-1680. (g) Banwell, M. G.; McRae, K. J. *Org. Lett.* **2000**, *2*, 3583-3586. (h) Dixon, D. J.; Foster, A. C.; Ley, S. V. *Org. Lett.* **2000**, *2*, 123-125. (i) Nishioka, T.; Iwabuchi, Y.; Irie, H.; Hatakeyma, S. *Tetrahedron Lett.* **1998**, *39*, 5597-5600.

(7) (a) Quinkert, G.; Fernholz, E.; Eckes, P.; Neumann, D.; Dürner, G. *Helv. Chim. Acta* **1989**, *72*, 1753-1786. (b) Enders, D.; Prokopenko, O. F. *Liebigs Ann.* **1995**, 1185-1191. (c) Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1997**, *62*, 377-386. (d) Kobayashi, Y.; Nakano, M.; Kumar, G. B.; Kishihara, K. *J. Org. Chem.* **1998**, *63*, 7505-7515. (e) Dubost, C.; Markó, I. E.; Ryckmanns, T. *Org. Lett.* **2006**, *8*, 5137-5140. (f) Reddy, C. R.; Rao, N. N.; Sujitha, P.; Kumar, C. G. *Eur. J. Org. Chem.* **2012**, 1819-1824. (g) Gandi, V. R. *Tetrahedron* **2013**, *69*, 6507-6511.

(8) (a) Quinkert, G.; Heim, N.; Glenneberg, J.; Billhardt, U.-M.; Autze, V.; Bats, J. W.; Dürner, G. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 362-364. (b) Quinkert, G.; Heim, N.; Glenneberg, J.; Döller, U.; Eichhorn, M.; Billhardt, U.-M.; Schwarz, C.; Zimmermann, G.; Bats, J. W.; Dürner, G. *Helv. Chim. Acta* **1988**, *71*, 1719-1794. (c) Quinkert, G.; Döller, U.; Eichhorn, M.; Küber, F.; Nestler, H. P.; Becker, H.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta* **1990**, *73*, 1999-2047. (d) Quinkert, G.; Becker, H.; Dürner, G. *Tetrahedron Lett.* **1991**, *32*, 7397-7400.

(9) Oppolzer, W.; Radinov, R. N.; De Brabander, J. *Tetrahedron Lett.* **1995**, *36*, 2607-2610.

(10) Raghavan, S.; Sreekanth, T. *Tetrahedron Lett.* **2006**, *47*, 5595-5597.

(11) (a) Schlünzen, F.; Zarivach, R.; Harms, J.; Bashat, A.; Tocilj, A.; Albrecht, R.; Yonath, A.; Franceschi, F. *Nature* **2001**, *413*, 814-821; (b) Tu, D.; Blaha, G.; Moore, P. B.; Steitz, T. A. *Cell* **2005**, *121*, 257-270; (c) Mankin, A. S. *Curr. Opin. Microbiol.* **2008**, *11*, 414-421.

(12) (a) Martin, S. F.; Hida, T.; Kym, P.R.; Loft, M.; Hodgson, A. *J. Am. Chem. Soc.* **1997**, *119*, 3193-3194. (b) Toshima, K.; Nozaki, Y.; Mukaiyama, S.; Tamai, T.; Nakata, M.; Tatsuta, K.; Kinoshita, M. *J. Am. Chem. Soc.* **1995**, *117*, 3717-3727. (c) Woodward, R. B.; Logusch, E.; Nambiar, K. P.; Saka, K.; Ward, D. E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L. J.; Card, P. J.; Chen, C. H.; Chênevert, R. B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D. G.; Hayakawa, K.; Heggie, W.; Hesson, D. P.; Hoppe, D.; Hoppe, I.; Hyatt, J. A.; Ikeda, D.; Jacobi, P. A.; Kim, K. S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V. J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R. S.; Ong, B. S.; Press, J. B.; Rajan Babu, T. V.; Rousseau, G.; Sauter, H. M.; Suzuki, M.; Tatsuta, K.; Tolbert, L. M.; Truesdale, E. A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A. T.; Vladuchick, W. C.; Wade, P. A.; Williams, R. M.; Wong, H. N.-C. *J. Am. Chem. Soc.* **1981**, *103*, 3215-3217.

(13) (a) Bestmann, H. J.; Sandmeier, D. *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 634. (b) Schobert, R.; Boeckman Jr., R. K.; Pero, J. E. *Org. Syntheses* **2005**, *82*, 140-143.

(14) (a) Löffler, J.; Schobert, R. *J. Chem. Soc., Perkin Trans. 1.* **1996**, 2799-2802. (b) Schobert, R.; Siegfried, S.; Gordon, G. J. *J. Chem. Soc., Perkin Trans. 1.* **2001**, 2393-2397. (c) Schobert, R.; Siegfried, S.; Nieuwenhuyzen, M.; Milius, W.; Hampel, F. *J. Chem. Soc., Perkin Trans. 1.* **2000**, 1723-1730.

(15) (a) Valente, C.; Belowich, M. E.; Hadei, N.; Organ, M. G. *Eur. J. Org. Chem.* **2010**, 4343-4354. (b) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 3805-3807. (c) Organ, M. J.; Avola, S.; Dubovyk, I.; Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Valente, C. *Chem. Eur. J.* **2006**, *12*, 4749-4755. (d) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *J. Org. Chem.* **2005**, *70*, 8503-8507.

(16) Brown, H. C.; Lane, C. F. *J. Am. Chem. Soc.* **1970**, *92*, 6660-6661.

(17) Huo, S. *Org. Lett.* **2003**, *5*, 423-425.

(18) (a) Flynn, E. H.; Sigal, M. V.; Wiley, P. F.; Gerzon, K. *J. Am. Chem. Soc.* **1954**, *76*, 3121-3131. (b) Bolton, C. H.; Foster, A. B.; Stacey, M.; Weber, J. M. *J. Chem. Soc.* **1961**, 4831-4836.

(19) (a) Zhang, Z.; Fukuzaki, T.; Myers, A. G. *Angew. Chem. Int. Ed.* **2016**, *55*, 523-527. (b) Korte, F.; Bilow, A.; Heinz, R. *Tetrahedron* **1962**, *18*, 657-666. (c) Newman, H. *J. Org. Chem.* **1964**, *29*, 1464-1468. (d) Richardson, A. C. *J. Chem. Soc.* **1964**, 5364-5370. (e) Baer, H. H.; Chiu, C.-W. *Can. J. Chem.* **1974**, *52*, 122-124. (f) Davidson, M. H.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 1601-1603. (g) Velvadapu, V.; Andrade, R. B. *Carbohydr. Res.* **2008**, *343*, 145-150.

(20) Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelmann, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, *29*, 2176-2179.

(21) Williams, D. B. G.; Lawton, M. *J. Org. Chem.* **2010**, *75*, 8351-8354.