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Carbohydrate-Based Macrolides Prepared via a Convergent Ring Closing Metathesis Approach: In Search for Novel Antibiotics

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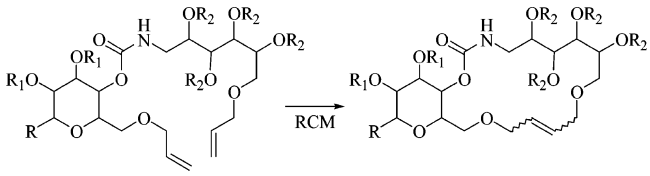

An efficient convergent approach has been developed for the construction of novel, nonnatural polysubstituted carbohydrate-based macrolides. A key step in the synthesis is the formation of the macrocyclic ring via a ring-closing metathesis reaction. The obtained macrolide analogues have been screened for biological activity against gram-positive and gram-negative bacteria, yeasts, and molds.

Introduction

It is assumed that complex natural products in general show a significantly higher propensity to display biological activity than small molecules do.[1] One of the reasons for this is their much larger "conformational space":[2] they can adopt a variety of conformations, thus increasing the chance to efficiently bind to one or more receptors. Macrolides fall into this category of large natural product molecules. These fungal metabolites are characterized by the presence of a macrocyclic lactone ring, usually linked to one or more neutral sugar moieties and/or amino sugars, and possess antimicrobial activity.[3] However, the widespread and intensive use of macrolide antibiotics has accelerated the natural selection of macrolide-resistant pathogens.[4] Accordingly, there is an increasing demand for second-generation macrolides, displaying restored activity. Research indicates that changes in the structure of antimicrobial drugs can circumvent the resistance of mutant microorganisms.[5] A straightforward and intrinsically simple approach is based on chemical modification of natural macrolides that are accessible in large quantities from fermentation by microorganisms. Modifications include acylation of hydroxy groups,[6] deacylation,[7] aldehyde or ketone reduction,[8] double bond reduction,[9] and N-demethylation.[10] More fundamental structural changes require synthesis of macrolide analogues from simple building blocks, and over the past few years four general approaches have been developed to control the critical stereochemistry:[11]

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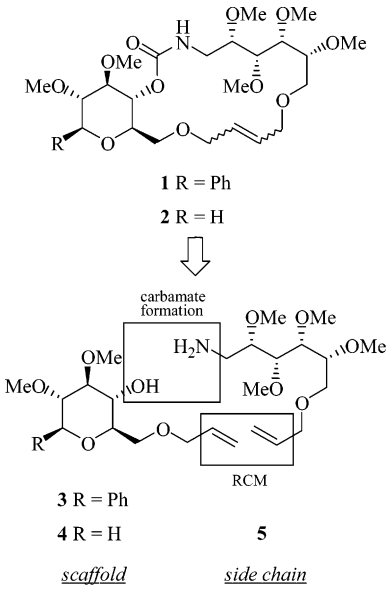
(i) ring-cleavage, where the appropriate stereorelationship of the asymmetric centers is first secured by using the conformational bias of a small or medium sized ring, which is then opened to give an acyclic fragment with the stereocenters correctly related,[12] (ii) exploitation of the existing asymmetric centers and functionalities of a carbohydrate precursor,[13] (iii) stereoselective introduction of new asymmetric centers on an acyclic precursor,[14] and (iv) stereoselective introduction of new asymmetric centers onto an intact macrocyclic precursor, using the conformational bias of the macrocycle.[15] Additional problems in the total synthesis of macrolide analogues are the macrolactonization step and the stereo- and regiocontrolled attachment of the appropriate basic or neutral deoxysugars.

We have developed a convergent synthetic approach for the construction of novel, nonnatural carbohydrate-based macrolide analogues.[16] Our strategy is inspired by the carbohydrate precursor method to control the stereochemistry of the target macrolides and basically consists of the following key steps: (i) the synthesis of a carbohydrate scaffold, (ii) attachment of an acyclic side chain, and (iii) final formation of the macrocyclic ring via a ring closing metathesis reaction. Previously, we reported the synthesis of carbohydrate-based macrolide analogues using simple, commercially available, aliphatic side chains to construct the macrocyclic ring.[17] Their interesting biological activity inspired us to prepare macrocycles with a more complex substitution pattern, to better resemble natural macrolides. We now wish to present the synthesis and biological activity of such macrolide analogues, consisting of a substituted macrocyclic ring fused to a carbohydrate scaffold. Functionalization of the macrocyclic ring was obtained by incorporation of a polyfunctional acyclic carbohydrate side chain in our convergent approach (Scheme 1). To limit the ring size, only one sugar chain was attached to the scaffold to construct the ring closing metathesis precursor. This dictated ring size and the position of the double bond after ring closure.

SCHEME 1. Retrosynthetic Analysis



Results and Discussion

Since the formation of the macrocyclic ring via a ring-closing metathesis (RCM) reaction represents the key step in our approach, one of the synthetic functions of the scaffold is to keep the side chains in the correct position to provide the necessary bias for ring closure.[18] Due to their cyclic nature, imposing a conformational restriction, pyranose and furanose sugars are ideally suited for this purpose. Moreover, carbohydrate substructures often occur in natural macrolides and can contribute significantly to the biological activity of macrolide compounds. In addition, the use of polyfunctional carbohydrate scaffolds not only offers an easy access to structural and configurational diversity, but also eliminates the need for the often problematic stereo- and regiocontrolled glycosylation after macrocyclization.

Starting from commercially available **6** two different scaffolds **3** and **4** were prepared (Scheme 2). The key feature of the reaction sequence is the application of a 4,6-*O*-prop-2-enylidene acetal as a protective group for the C4 and C6 hydroxyl functions. Selective reductive opening[19] of this functionality not only releases a free hydroxyl group at C4, which can be used for attachment of the side chain via a carbamate bond, but also generates an allyl ether at C6 providing one of the double bonds required for RCM. Scaffolds **3** and **4** lack a glycosidic bond and should have increased metabolic stability compared to natural carbohydrates.

Treatment of **6** with hydrogen bromide in acetic acid led to selective conversion of the anomeric acetate into a bromide, providing a good leaving group for Grignard substitution with phenylmagnesium bromide.[20] Reacetylation of the deprotected hydroxyl groups and subsequent crystallization of the crude product from 2-propanol furnished **7**. Deacetylation finally gave **8** in 66% overall yield starting from **6**. The enhanced reactivity of the anomeric acetate also allowed selective exchange with thiophenol under acidic conditions, exclusively affording **11** due

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(13) See, e.g.: (a) Tatsuta, K.; Anemiya, Y.; Maniwa, S.; Kinoshita, M. *Tetrahedron Lett.* **1980**, *21*, 2837−2840. (b) Tatsuta, K.; Yamanuchi, T.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3035−3038. (c) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1222−1224. (d) Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 1224−1226. (e) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *Tetrahedron Lett.* **1979**, *20*, 2327−2330.

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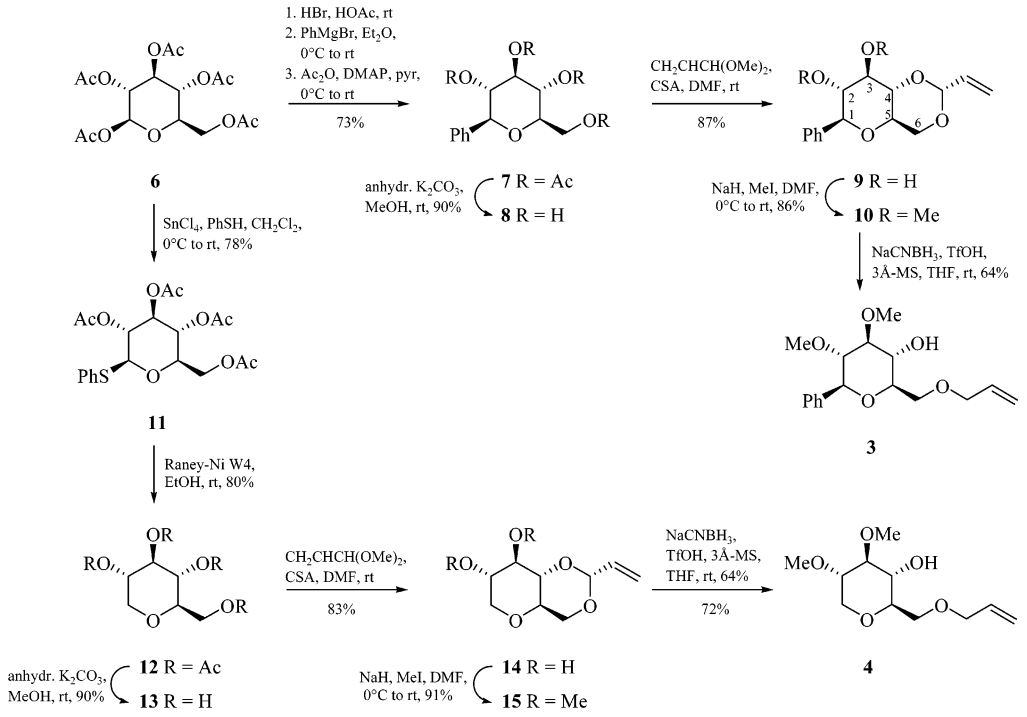
SCHEME 2. Synthesis of the Scaffolds

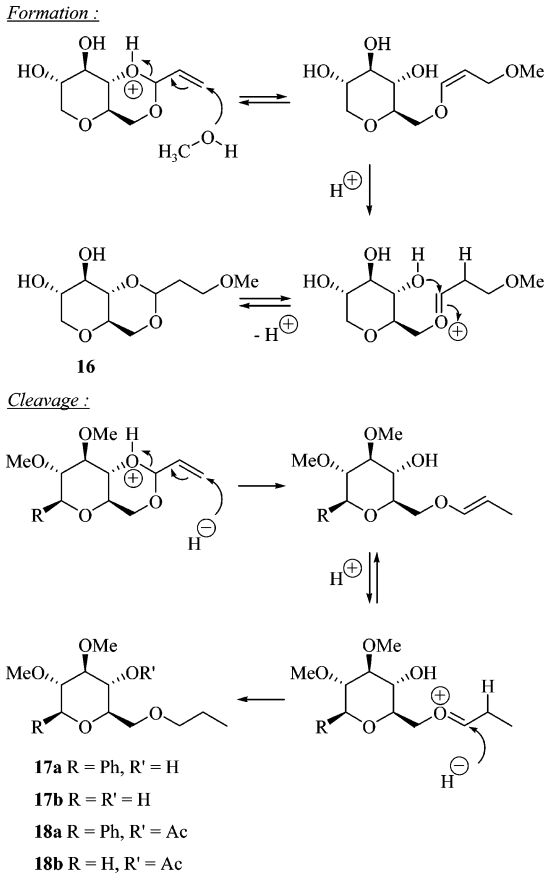


to neighboring group participation (J_{H1-H2} = 10.1 Hz).[21] Reductive cleavage of the thiophenyl group with freshly prepared Raney nickel under inert atmosphere,[22] followed by methanolysis of the acetates, led to 1,5-anhydro-D-glucitol **13** in 56% overall yield from **6**. Acid-catalyzed protection of the primary hydroxyl function and the secondary alcohol function at C4 in **8** and **13** as a 4,6-*O*-prop-2-enylidene acetal, subsequent methylation of the two remaining hydroxyl groups under Williamson conditions, and, finally, regioselective reductive ring opening of the acetal afforded scaffolds **3** and **4**, respectively.

A strong NOE enhancement of both H4 (δ = 3.45) and $H6_{ax}$ (δ = 3.40) upon irradiation of the acetal proton (δ = 4.83) was observed for **10**, indicating an axial orientation of the acetal proton (for numbering of the protons, see Scheme 2, structure **10**).[23] A similar NOE effect was observed for compound **15**, between the acetal proton (δ = 4.73) and H4 (δ = 3.28) and $H6_{ax}$ (δ = 3.31), demonstrating also in this case the formation of the thermodynamically favored epimer. The formation of only one acetal isomer is remarkable, since a cis/trans mixture has been reported in related cases.[24]

1,3-Dioxolanes and 1,3-dioxanes are the most common protective groups for 1,2- and 1,3-diols and the reaction conditions for their introduction, cleavage, and regioselective ring opening are well established.[25] However, we observed unexpected side reactions during formation and reductive cleavage of **10** and **15** (Scheme 3). These acetals are derived from an α,β-unsaturated aldehyde (acrolein), and byproducts arise from addition of nucleophiles to the activated acetal to give conjugate addition products, in a reaction similar to the Michael reaction. Preparation of **14**, for example, was disturbed

SCHEME 3. Side Reactions during Formation and Cleavage of 4,6-*O*-Prop-2-enylidene Acetals



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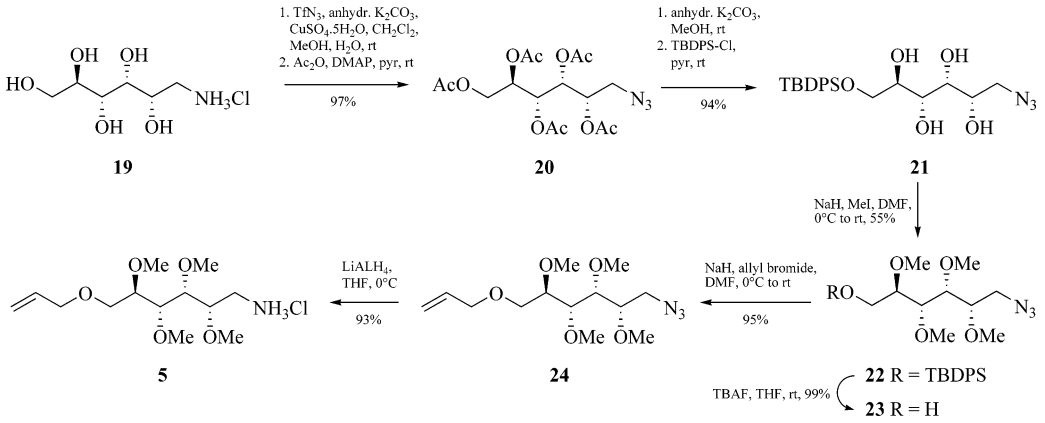
SCHEME 4. Synthesis of the Polyfunctionalized Side Chain 5



by the 1,4-addition of methanol, liberated from acrolein dimethyl acetal in the reaction mixture, to the activated acetal, leading to the undesired formation of 3-methoxypropylidene acetal **16**. A similar side reaction led to a decreased yield for the regioselective reductive cleavage of acetals **10** and **15** (Scheme 3). According to the literature, 4,6-*O*-prop-2-enylidene acetals derived from glycopyranoses behave in the same way as 4,6-*O*-benzylidene acetals when treated with $NaCNBH_3$/HCl/THF, giving predominantly the 6-*O*-allyl ethers with a free 4-OH functionality.[19] For enhanced reproducibility, we replaced HCl with TfOH[26] to effect regioselective ring opening of prop-2-enylidene acetals **10** and **15**. These reaction conditions led to the formation of a significant amount (about 15%) of 6-*O*-propyl ethers **17a** and **17b**, respectively, via 1,4-addition of a hydride to the activated acetal. Acetylation of both products with Ac_2O/pyridine resulted in a downfield shift of one proton (H4), confirming the position of the propyl ether at C6. To our knowledge, these side reactions have not been reported in the literature before.

Highly functionalized aminopolyol side chains can be prepared from amino alditols. The latter are easily accessible via reductive amination of commercially available monosaccharides.[27] The configuration of the resulting polysubstituted acyclic side chain is determined by the cyclic precursor, and a diverse set of side chains can be obtained. As a typical example, commercially available 1-amino-1-deoxy-D-glucitol hydrochloride **19** is transformed into side chain **5** (Scheme 4). Conversion of the amino function into azide **20**, applying the procedure of Wong,[28] allowed subsequent selective protection of the primary and secondary hydroxyl groups. Deprotection of pentaacetate **20**, followed by selective silylation of the primary alcohol, furnished compound **21**. Methylation of the remaining free secondary hydroxyl functions led to intermediate **22**, which upon treatment with TBAF afforded the primary alcohol **23** in nearly quantitative yield. The double bond required for RCM was introduced by alkylation of alcohol **23** with allyl bromide. Final reduction of azide **24** with $LiAlH_4$ regenerated the amine function required for coupling of the side chain with the scaffold via a carbamate bond. Thus, side chain building block **5** was obtained as its hydrochloride salt in 6 steps from **19** in 44% overall yield.

The efficiency of this general procedure was decreased by the unexpected 1,2- and 1,3-migration of the TBDPS ether[29] during methylation of tetrol **21** under basic conditions. LC-MS analysis of the isomeric mixture indicated the formation of approximately 19% 1,2-migration product and about 1% 1,3-migration product. The desired silyl ether **22** proved to be nearly inseparable from both migration products, but after deprotection of the silyl ether a mixture of primary and secondary alcohols was obtained, with enough structural dissimilarities to allow separation by flash column chromatography on silica gel.

Next, we examined formation of a carbamate bond between the amine function of **5** and the secundary alcohol function in scaffolds **3** and **4** (Scheme 5). DMAP-catalyzed treatment of scaffold **3** with disuccinimidyl carbonate (DSC) in DMF gave activated carbonate **25** in high yield.[30] Nucleophilic displacement of the *N*-hydroxysuccinimidyl leaving group with side chain **5** smoothly provided RCM precursor **26**, in 91% yield from alcohol **3**. The macrocyclization reaction of diene **26** with the first generation Grubbs' catalyst in CH_2Cl_2 at room temperature proceeded as planned. This indicates that key parameters for RCM, such as the distance between the alkene units and the polar carbamate, as well as their relative orientation and affinity, are properly assessed in our strategy and provide the necessary bias for ring closure.[18] As expected, formation of the macrocyclic ring produced a mixture of *E*- and *Z*-isomers **1a** and **1b**. While normal and reversed phase chromatography were inadequate to effect good separation, silver nitrate impregnated silica gel[31] gave excellent results, affording pure **1a** and **1b** in a 3.7/1 ratio. Applying a similar synthetic route, scaffold **4** afforded pure *E*- and *Z*-alkene **2a** and **2b**, respectively, in a 7.2/1 ratio.

The geometry of the double bond in **1a**, **1b**, **2a**, and **2b** was deduced from the vinylic vicinal coupling constants in the ^1H NMR spectra. For all four compounds, the signals from the

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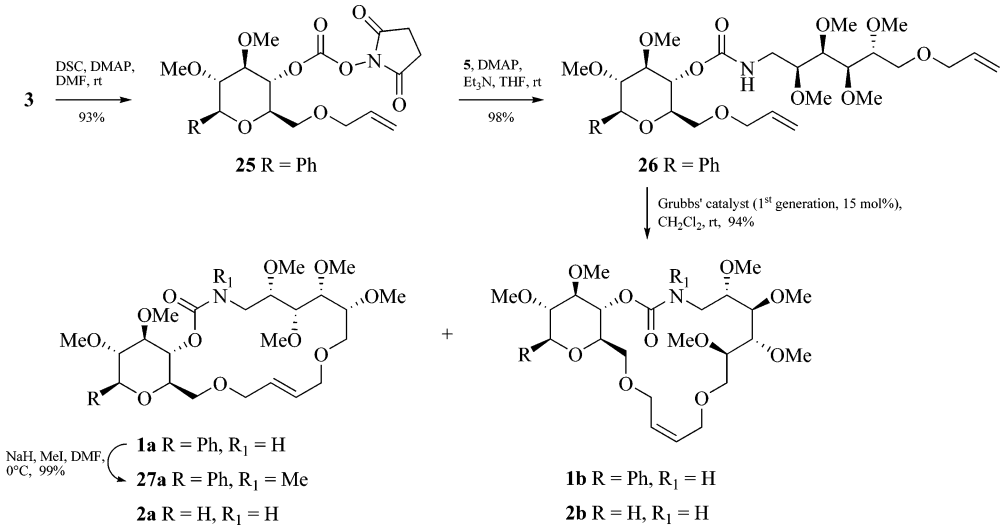
SCHEME 5. Ring Closing Metathesis



vinylic protons were better resolved when the spectrum was recorded in benzene-d_6, but only for **2b** was it not possible to calculate the vinylic vicinal coupling constants from the spectrum obtained in chloroform-*d*. Macrolides **1a** and **2a** displayed large coupling constants (15−16 Hz), supporting the *E*-geometry for the double bond. On the other hand, **1b** and **2b** showed significantly smaller coupling constants (11−12 Hz), indicating the *Z*-geometry for the double bond. Most signals in the ^{1}H NMR spectra of the macrolides **1a**, **1b**, **2a**, and **2b** were slightly broadened. A possible explanation for these irregularities is the occurrence of cis/trans carbamate isomerization. Although amides and carbamates share common features, the additional oxygen of the carbamate functionality exerts unique steric and electronic perturbations. One consequence is that the barriers for rotation in carbamates are usually 3−4 kcal/mol (about 15−20%) lower than those in the corresponding amides, provoking a less pronounced broadening of ^{1}H NMR signals.[32] To be able to attribute the line broadening in the ^{1}H NMR spectra of macrocycles **1a**, **1b**, **2a**, and **2b** to this cis/trans carbamate isomerization, we had to calculate the free energy of activation for rotation from the NMR spectra, in order to compare the value with reported energy barriers for carbamate bond rotation. Since these calculations are based on the temperature-dependent fusion of two separate signals from a proton exchanging slowly between two conformers, we first attempted to increase the rotational barrier. We envisaged that *N*-alkylation of the carbamate would increase the energy of activation for rotation, slowing down the rate of exchange between different magnetic environments sufficiently to cause protons of the two conformers to appear as fully separated signals. Indeed, upon *N*-methylation of macrolide **1a** the ^{1}H NMR spectrum of the corresponding carbamate **27a** displayed not only enhanced line broadening, but also the emergence of smaller twin signals. The isolated position of the twin signals originating from H4 (for numbering, see Scheme 2, **10**) of the scaffold enabled us to do a rough calculation of the free energy of activation for rotation.

When the two magnetic environments are equally populated, the rate constant at the coalescence point is given by eq 1, where $\Delta\nu$ is the frequency separation of the initially sharp lines. NMR experiments at elevated temperature allowed us to determine the coalescence temperature T_c. The free energy of activation for rotation is now given by eq 2, where the coalescence temperature T_c is expressed in Kelvin and R is the gas constant.[33]

$$k = \pi\Delta\nu/2^{1/2}\ \mathrm{s}^{-1} \quad (1)$$

$$\Delta G^{\#} = RT_c[23 + \ln(T_c/\Delta\nu)]\ \mathrm{kJ\ mol}^{-1} = RT_c[23 + 2.3\log(T_c/\Delta\nu)]\ \mathrm{kJ\ mol}^{-1} \quad (2)$$

Although the calculated free energy of activation for rotation ($\Delta G^{\#} \approx 16$ kcal mol^{-1}) is remarkably consistent with the reported barriers for carbamate bond rotation,[33] it should be emphasized that our calculations are based on strong simplifications neglecting the unequal population of both environments, and, therefore, possess only an indicative value. Nevertheless, the results indicate that the distinct line broadening in the ^{1}H NMR spectra of compounds **1a**, **1b**, **2a**, and **2b** may originate from cis/trans carbamate isomerization.

The biological activities of macrolides **1a**, **1b**, **2a**, and **2b** toward gram-negative bacteria (*E. coli* and *P. aeruginosa*), gram-positive bacteria (*S. aureus*, *E. faecalis*, and *C. perfringens*), yeasts (*C. albicans* and *C. neoformans*), and molds (*A. fumigatus* and *T. mentagrophytes*) were evaluated applying well-established assay techniques[34] (see the Supporting Information for details). None of the screened compounds showed any significant activity against bacteria (Table 1). Macrolides **1a**, **1b**, **2a**, and **2b** displayed a moderate activity against *C. neoformans* (40−50% growth inhibition at 25 ppm), and **1b**, **2a**, and **2b** to a lesser extent against *A. fumigatus* (20−30% growth inhibition at 25 ppm). Analogues **1a** and **1b** showed a mild general activity against yeasts, in particular *C. neoformans*.

In conclusion, we developed a highly convergent and flexible approach for the construction of polysubstituted macrolide

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(34) Methods are based on the NCCLS (Clinical and Laboratory Standard Institute) documents M7-A4 (for bacteria), M27-A (for yeasts), and M38-A (for molds) for the screening of the antimicrobial activity of different compounds with broth microdilution techniques. An automated Bioscreen C system was used.

TABLE 1. Antibacterial and Antifungal Activity of the Macrolide Analogues 1a, 1b, 2a, and 2b[34]

	% of growth at a dose of 25 ppm compared to the negative control[a]								
sample	*E. coli*	*P. aeruginosa*	*S. aureus*	*E. faecalis*	*C. perfringens*	*C. albicans*	*C. neoformans*	*A. fumigatus*	*T. mentagrophytes*
control	100	100	100	100	100	100	100	100	100
1a	95.6	94.7	91.9	95.0	97.6	88.0	54.1	94.0	87.0
1b	95.8	94.7	92.4	95.9	99.6	80.3	58.4	80.0	92.0
2a	95.8	93.7	93.0	95.5	96.5	100	56.1	69.0	95.0
2b	96.1	94.7	93.5	93.7	99.2	94.4	51.2	78.0	92.0

[a] Average values from five experiments, expressed as the ratio (in %) of the area under the growth curve of the test sample compared to the negative control.

analogues. A diverse set of macrolides, differing in stereochemistry and/or in the number of carbon atoms and hydroxyl groups, is accessible depending on the choice of the carbohydrate starting materials. The key step in our strategy is the formation of the macrocyclic ring via a ring-closing metathesis reaction. All target macrocycles are obtained in good overall yields. However, in contrast with the unsubstituted carbohydrate-based macrolides we reported earlier,[17] their antibiotic activity is quite poor.

Experimental Section

Synthesis of 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylbenzene (7). A solution of **6** (12.3 g, 31.50 mmol) in HBr (30% in HOAc; 50 mL) was stirred for 30 min under argon atmosphere at 25 °C. After evaporation of the solvent under reduced pressure, residual traces of HOAc were removed by azeotropic evaporation with toluene (4 × 25 mL), and the residue was dried under high vacuum. The crude 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide was obtained as a yellow solid, and used in the next step without further purification: R_f 0.46 (cyclohexane−EtOAc 1/1); IR (film) 2962, 2360, 2342, 1748, 1435, 1369, 1218, 1162, 1112, 1079, 1042 cm^{-1}; ES-MS (*m*/*z*) 433 [M + Na]$^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (1H, d, J = 4.0 Hz), 5.56 (1H, t, J = 9.7 Hz), 5.16 (1H, t, J = 9.7 Hz), 4.84 (1H, dd, J = 4.0, 10.0 Hz), 4.33 (1H, m), 4.30 (1H, m), 4.13 (1H, dd, J = 1.5, 12.3 Hz), 2.11 (3H, s), 2.10 (3H, s), 2.05 (3H, s), 2.03 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 169.7, 169.6, 169.3, 86.3, 71.9, 70.4, 69.9, 66.9, 60.8, 20.5, 20.5, 20.4, 20.4.

A solution of the crude 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl bromide in Et_2O (250 mL) was added to a mechanically stirred solution of PhMgBr (3 M in Et_2O; 100 mL, 300 mmol) in Et_2O (250 mL) at 0 °C. The mixture was allowed to warm to 25 °C, and stirring was continued for 70 h. The mixture was poured slowly into H_2O (1000 mL), containing HOAc (100 mL), and the organic and the aqueous layer were separated. The organic phase was washed with H_2O (3 × 250 mL), and the combined aqueous layers were concentrated under reduced pressure. The residue was dissolved in pyridine (250 mL), and Ac_2O (170 mL) and DMAP (100 mg, 0.82 mmol) were slowly added at 0 °C. After the mixture was stirred for 24 h at 25 °C, pyridine and Ac_2O were removed by evaporation under reduced pressure. The residue was dissolved in Et_2O (1500 mL) and washed with saturated $NaHCO_3$ (2 × 500 mL), 1 M HCl (2 × 500 mL), and H_2O (2 × 500 mL). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product (11.6 g) was crystallized from 2-propanol, and the mother liquor was purified by flash column chromatography (CH_2Cl_2−acetone 99/1). 2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylbenzene (**7**) (combined: 9.391 g, 73%) was obtained as a white solid: R_f 0.42 (cyclohexane−EtOAc 1/1); mp 149−150 °C; IR (film) 2956, 1753, 1433, 1368, 1224, 1104, 1036 cm^{-1}; ES-MS (*m*/*z*) 431 [M + Na]$^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (5H, m), 5.24 (1H, t, J = 9.4 Hz), 5.24 (1H, t, J = 9.8 Hz), 5.14 (1H, t, J = 9.8 Hz), 4.40 (1H, d, J = 9.9 Hz), 4.30 (1H, dd, J = 4.7, 17.2 Hz), 4.16 (1H, dd, J = 1.5, 12.2 Hz), 3.85 (1H, m), 2.09 (3H, s), 2.06 (3H, s), 2.01 (3H, s), 1.80 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.3, 169.4, 168.7, 136.0, 128.8, 128.3, 127.0, 80.1, 75.9, 74.1, 72.4, 68.4, 62.2, 20.6, 20.5, 20.2.

Synthesis of β-D-Glucopyranosylbenzene (8). Anhydrous K_2CO_3 (2.45 g, 17.70 mmol) was added to a stirred solution of tetraacetate **7** (28.92 g, 70.81 mmol) in THF (360 mL) and MeOH (360 mL). Stirring was continued at 25 °C for 18 h. Then, silica gel (50 g) was added, and the solvent was removed under reduced pressure. The residue was chromatographed (cyclohexane−acetone−MeOH 10/10/1) to yield **8** (15.31 g, 90%) as a white foam: R_f 0.19 (cyclohexane−acetone−MeOH 10/10/1); IR (film) 3368, 2919, 2360, 1636, 1496, 1455, 1082, 1042 cm^{-1}; ES-MS (*m*/*z*) 258 [M + NH_4]$^+$, 263 [M + Na]$^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (2H, d, J = 7.1 Hz), 7.35 (2H, t, J = 7.6 Hz), 7.30 (1H, m), 4.15 (1H, d, J = 9.4 Hz), 3.90 (1H, dd, J = 1.6, 12.1 Hz), 3.72 (1H, dd, J = 5.2, 12.0 Hz), 3.51 (1H, t, J = 8.7 Hz), 3.45 (1H, t, J = 9.4 Hz), 3.43 (3H, m), 3.40 (1H, t, J = 9.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3, 127.4, 82.4, 80.7, 78.2, 75.0, 70.4, 61.4.

Synthesis of (*R*)-4,6-*O*-Prop-2-enylidene-β-D-glucopyranosylbenzene (9). Acrolein dimethyl acetal (2.59 mL, 21.92 mmol) and CSA (0.42 g, 1.824 mmol) were added to a stirred solution of tetrol **8** (1.752 g, 7.29 mmol) in DMF (12 mL). Stirring was continued at 25 °C for 24 h. The reaction was quenched with Et_3N (305 μL, 2.188 mmol) and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography (CH_2Cl_2−*i*PrOH 97/3) to yield **9** (1.77 g, 87%) as a white foam: R_f 0.22 (CH_2Cl_2−*i*PrOH: 97/3); $[\alpha]^{20}_D$ +13.2 (*c* 1.01, $CHCl_3$); IR (film) 3407, 2878, 1659, 1103, 1078, 1010 cm^{-1}; EI-MS (*m*/*z*) 57 (86), 77 (47), 91 (97), 107 (100), 120 (18), 143 (10), 179 (15), 277 (<1, M$^+$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (4H, br d, J = 4.4 Hz), 7.34 (1H, m), 5.88 (1H, ddd, J = 4.6, 10.7, 17.4 Hz), 5.53 (1H, dt, J = 1.2, 17.4 Hz), 5.35 (1H, dt, J = 1.1, 10.7 Hz), 5.04 (1H, d, J = 4.6 Hz), 4.26 (1H, d, J = 9.4 Hz), 4.25 (1H, m), 3.87 (1H, t, J = 8.7 Hz), 3.62 (2H, m), 3.52 (2H, m), 3.05 (1H, br s), 2.37 (1H, br s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 134.2, 129.6, 129.5, 128.3, 120.5, 101.8, 83.5, 81.5, 76.6, 75.6, 71.6, 69.3. HRMS (EI) calcd for $C_{15}H_{19}O_5$ 279.1233, found 279.1225 [M + H]$^+$.

Synthesis of 2,3-Di-*O*-methyl-(*R*)-4,6-*O*-prop-2-enylidene-β-D-glucopyranosylbenzene (10). NaH (60% dispersion in mineral oil; 0.954 g, 23.86 mmol) was added to a stirred solution of diol **9** (1.66 g, 5.97 mmol) in DMF (60 mL) at 0 °C. After the mixture was stirred at 0 °C for 30 min, MeI (1.86 mL, 29.83 mmol) was added. The cooling was removed, and stirring was continued at 25 °C for 21 h. The mixture was then poured into H_2O (1000 mL), the two layers were separated, and the water layer was extracted with Et_2O (3 × 500 mL). The combined organic layers were washed with brine (500 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed (*n*-pentane−Et_2O 5/1) to afford dimethyl ether **10** (1.56 g, 86%) as a white solid: R_f 0.21 (*n*-pentane−Et_2O 5/1); mp 68−70 °C; $[\alpha]^{20}_D$ −6.5 (*c* 1.05, $CHCl_3$); IR (film) 2934, 2890, 2835, 1167, 1102, 1042, 1032, 1002 cm^{-1}; EI-MS (*m*/*z*): 88 (58), 99 (22), 121 (100), 185 (11), 207 (34), 306 (<1, M$^+$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−

7.40 (5H, m), 5.90 (1H, ddd, J = 4.0, 10.8, 17.4 Hz), 5.53 (1H, dt, J = 1.3, 17.4 Hz), 5.35 (1H, dt, J = 1.2, 10.8 Hz), 5.04 (1H, d, J = 4.0), 4.25 (1H, dd, J = 4.6, 10.4 Hz), 4.22 (1H, d, J = 9.6 Hz), 3.66 (3H, s), 3.62 (1H, t, J = 10.2), 3.52 (1H, t, J = 8.9), 3.48 (1H, m), 3.47 (1H, m), 3.16 (1H, dd, J = 8.3, 9.4 Hz), 3.04 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.5, 134.5, 129.3, 128.3, 119.9, 101.2, 86.5, 85.2, 83.2, 82.4, 71.5, 69.4, 61.8, 61.6. HRMS (EI) calcd for $C_{17}H_{23}O_5$ 307.1546, found 307.1539 $[M + H]^+$.

Synthesis of 6-*O*-Allyl-2,3-di-*O*-methyl-β-D-glucopyranosylbenzene (3). TfOH (2.44 mL, 27.54 mmol) was added *cautiously* via a syringe pump (100 μL/minute) to a stirred mixture of activated molecular sieves (3 Å, 1.6 mm pellets; 1.140 g), $NaCNBH_3$ (1.80 g, 27.16 mmol), and acetal **10** (1.140 g, 3.72 mmol) in THF (37 mL) at 25 °C. After addition, the mixture was stirred for another 30 min, before being poured into H_2O (250 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 250 mL), and the combined organic fractions were washed with brine (250 mL). The organic layer was dried over $MgSO_4$ and filtered through a pad of silica gel. The solvent was removed under reduced pressure, and the residue was chromatographed (*n*-pentane−acetone 85/15) to afford **3** (0.735 g, 64%) and **17a** (0.169 g, 15%) as colorless oils. Data for **3**: R_f 0.20 (*n*-pentane−acetone 85/15); $[\alpha]^{20}_D$ −16.2 (*c* 1.07, $CHCl_3$); IR (film) 3420, 2976, 2932, 2905, 2867, 2834, 1145, 1088, 1070 cm^{-1}; ES-MS (*m*/*z*) 41 (38), 73 (20), 88 (75), 121 (100), 147 (11), 207 (10), 308 (<1, M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (2H, br d, J = 6.5 Hz), 7.33 (3H, m), 5.89 (1H, ddd, J = 5.6, 10.4, 17.2 Hz), 5.27 (1H, dd, J = 1.6, 17.2 Hz), 5.18 (1H, dd, J = 1.3, 10.4 Hz), 4.14 (1H, d, J = 9.5 Hz), 4.08 (1H, ddt, J = 1.3, 5.6, 12.9 Hz), 4.04 (1H, ddt, J = 1.3, 5.6, 12.9 Hz), 3.76 (1H, dd, J = 4.9, 10.4 Hz), 3.72 (1H, dd, J = 4.4, 10.4 Hz), 3.68 (3H, s), 3.66 (1H, dt, J = 1.9, 9.2 Hz), 3.56 (1H, p, J = 4.7 Hz), 3.28 (1H, t, J = 8.9 Hz), 3.08 (1H, t, J = 9.2 Hz), 2.97 (1H, br d, J = 1.9 Hz), 2.94 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 134.4, 128.3, 128.2, 127.5, 117.4, 87.7, 85.9, 81.6, 77.9, 72.7, 72.4, 70.8, 61.1, 60.1. Anal. Calcd for $C_{17}H_{24}O_5$: C, 66.21; H, 7.84. Found: C, 66.16; H, 7.95. Data for **17a**: R_f 0.24 (*n*-pentane−acetone 85/15); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28−7.41 (5H, m), 4.14 (1H, d, J = 9.5 Hz), 3.77 (1H, dd, J = 4.8, 10.1 Hz), 3.70 (3H, s), 3.67 (2H, m), 3.56 (1H, p, J = 4.9 Hz), 3.49 (1H, dt, J = 6.6, 9.4 Hz), 3.45 (1H, dt, J = 6.6, 9.4 Hz), 3.29 (1H, t, J = 8.9 Hz), 3.24 (1H, d, J = 1.4 Hz), 3.09 (1H, t, J = 9.3 Hz), 2.96 (3H, s), 1.60 (2H, s, J = 7.1 Hz), 0.91 (3H, t, J = 7.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1, 128.3, 128.2, 127.5, 87.6, 85.7, 81.6, 77.3, 73.8, 73.3, 72.0, 61.1, 60.1, 22.8, 10.6. HRMS (EI) calcd for $C_{17}H_{27}O_5$ 311.1858, found 311.1850 $[M + H]^+$.

Synthesis of Phenyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (11). Thiophenol (43.5 mL, 0.423 mol) and $SnCl_4$ (50.0 mL, 0.268 mmol) were added to a stirred solution of **6** (150.0 g, 0.384 mol) in CH_2Cl_2 (1.65 l) at 0 °C. Stirring was continued at 0 °C for 15 min, and then at 25 °C for 24 h. The mixture was diluted with CH_2Cl_2 (0.5 L), and washed with 1 N HCl (2 × 2 L), saturated $NaHCO_3$ (2 × 2 L) and brine (2 × 2 L). The organic layer was dried over $MgSO_4$ and filtered, and the solvent was removed under reduced pressure. The crude product was purified by crystallization from *n*-pentane−CH_2Cl_2 to yield phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (**11**) (131.2 g, 78%) as a white solid: R_f 0.31 (*n*-hexane−EtOAc 6/4); mp 113−114 °C; $[\alpha]^{20}_D$ −100.9 (*c* 1.12, $CHCl_3$); IR (film) 1749, 1477, 1437, 1369, 1226, 1087, 1036 cm^{-1}; ES-MS (*m*/*z*) 463 $[M + Na]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (2H, m), 7.31 (3H, m), 5.22 (1H, t, J = 9.4 Hz), 5.04 (1H, t, J = 9.8 Hz), 4.97 (1H, t, J = 9.7 Hz), 4.70 (1H, d, J = 10.1 Hz), 4.22 (1H, dd, J = 5.1, 12.3 Hz), 4.18 (1H, dd, J = 2.5, 12.3 Hz), 3.73 (1H, ddd, J = 2.5, 5.1, 10.1 Hz), 2.09 (3H, s), 2.08 (3H, s), 2.01 (3H, s), 1.99 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.4, 170.0, 169.3, 169.1, 133.0, 131.6, 128.8, 128.3, 85.7, 75.7, 73.9, 69.9, 68.7, 62.1, 20.6, 20.4. Anal. Calcd for $C_{20}H_{24}O_9S$: C, 54.54; H, 5.49. Found: C, 54.56; H, 5.01.

Synthesis of 1,5-Anhydro-2,3,4,6-tetra-*O*-acetyl-D-glucitol (12). Thioglucoside **11** (2.665 g, 6.05 mmol) was added to a suspension of freshly prepared Raney nickel W4 (26 g) in absolute EtOH (100 mL). The mixture was stirred for 30 min at 25 °C, before the catalyst was removed by filtration through a celite pad. The catalyst was washed with absolute EtOH (3 × 50 mL) and the filtrate was concentrated under reduced pressure. The residue was chromatographed (cyclohexane−EtOAc 6/4) to yield **12** (1.608 g, 80%) as a white solid: R_f 0.25 (cyclohexane−EtOAc 6/4); mp 65−66 °C; $[\alpha]^{20}_D$ +39.1 (*c* 1.06, $CHCl_3$); IR (film) 1747, 1228, 1103, 1061, 1034 cm^{-1}; EI-MS (*m*/*z*) 43 (100), 332 (<1, M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.19 (1H, t, J = 9.5 Hz), 5.02 (1H, t, J = 9.7 Hz), 5.00 (1H, ddd, J = 5.7, 9.5, 10.4 Hz), 4.19 (1H, dd, J = 4.9, 12.4 Hz), 4.15 (1H, dd, J = 5.7, 11.3 Hz), 4.12 (1H, dd, J = 2.1, 12.4 Hz), 3.58 (1H, ddd, J = 2.2, 4.9, 10.0 Hz), 3.29 (1H, t, J = 11.0 Hz), 2.09 (3H, s), 2.03 (6H, s), 2.02 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 171.2, 170.7, 170.4, 77.3, 74.5, 69.8, 69.2, 67.7, 63.0, 21.6, 21.6, 21.5. HRMS (EI) calcd for $C_{14}H_{21}O_9$ 333.1186, found 333.1174 $[M + H]^+$.

Synthesis of 6-*O*-Allyl-1,5-anhydro-2,3-di-*O*-methyl-D-glucitol (4). Following the same procedures as for preparation of **3** from **7**, but starting from tetraacetate **12**, successive deacetylation, introduction of the prop-2-enylidene acetal, methylation of the remaining free hydroxyl groups, and final reductive opening of the acetal furnished alcohol **4** as an oil: R_f 0.19 (*n*-pentane−acetone 85/15); $[\alpha]^{20}_D$ +25.6 (*c* 1.13, $CHCl_3$); IR (film) 3462, 2970, 2937, 2914, 2861, 1463, 1357, 1161, 1128, 1084 cm^{-1}; EI-MS (*m*/*z*) 41 (86), 71 (100), 87 (57), 101 (33), 201 (<1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 (1H, ddt, J = 5.8, 10.4, 17.2 Hz), 5.27 (1H, dd, J = 1.5, 17.2 Hz), 5.19 (1H, dd, J = 1.5, 10.4 Hz), 4.09 (1H, dd, J = 5.1, 11.2 Hz), 4.03 (2H, m), 3.69 (1H, dd, J = 3.3, 10.4 Hz), 3.65 (3H, s), 3.61 (1H, dd, J = 5.4, 10.4 Hz), 3.45 (3H, s), 3.45 (1H, m), 3.36 (1H, ddd, J = 3.3, 5.4, 9.2 Hz), 3.29 (1H, ddd, J = 5.1, 8.8, 11.0 Hz), 3.15 (1H, t, J = 11.0 Hz), 3.11 (1H, t, J = 8.8 Hz), 2.72 (1H, d, J = 2.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.4, 117.7, 87.0, 79.8, 78.6, 72.7, 70.9, 70.1, 67.6, 60.9, 58.4. Anal. Calcd for $C_{11}H_{20}O_5$: C, 56.88; H, 8.68. Found: C, 56.66; H, 8.90.

Synthesis of 1-Azido-1-deoxy-2,3,4,5,6-penta-*O*-acetyl-D-glucitol (20). CH_2Cl_2 (25 mL) was added to a solution of NaN_3 (5.98 g, 91.9 mmol) in H_2O (15 mL). This heterogeneous mixture was cooled to 0 °C and stirred vigorously, while $(CF_3SO_2)O$ (3.1 mL, 18.38 mmol) was slowly added over 5 min. The mixture was allowed to stir vigorously for 2 h at 0 °C before both layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 12.5 mL), and the combined organic fractions (~50 mL) were washed with saturated Na_2CO_3 (50 mL). The organic phase was added to a sirred solution of amino glucitol **19** (2.0 g, 9.19 mmol), anhydrous K_2CO_3 (1.90 g, 13.79 mmol), and $CuSO_4 \cdot 5H_2O$ (23 mg, 91.9 μmol) in a mixture of H_2O (30 mL) and MeOH (60 mL). More MeOH was added to obtain a homogeneous solution (about 20 mL). The reaction mixture was stirred for 18 h at 25 °C, and then it was concentrated under reduced pressure (water bath <50 °C). The residue was dissolved in pyridine (75 mL), and Ac_2O (45 mL) and DMAP (100 mg, 0.82 mmol) were added. This solution was stirred for 3 h at 25 °C. After evaporation of the solvent under reduced pressure, residual traces of pyridine and Ac_2O were removed by azeotropic evaporation with toluene (100 mL). The residue was dissolved in EtOAc (200 mL) and washed with H_2O (3 × 100 mL). The organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by chromatography (cyclohexane−EtOAc 65/35) to yield azide **20** (3.70 g, 97%) as a white solid: R_f 0.21 (cyclohexane−EtOAc 7/3); mp 70−71 °C; $[\alpha]^{20}_D$ +7.3 (*c* 1.05, $CHCl_3$); IR (film) 2107, 1748, 1372, 1216, 1033 cm^{-1}; EI-MS (*m*/*z*) 43 (100); ES-MS (*m*/*z*) 440 $[M + Na]^+$; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.47 (1H, dd, J = 3.5, 7.2 Hz), 5.33 (1H, dd, J = 3.5, 7.7 Hz), 5.08 (1H, ddd, J = 3.9, 5.3, 7.2 Hz), 5.05 (1H, ddd, J = 3.2, 5.0, 7.7 Hz), 4.23 (1H, dd, J = 3.2, 12.5 Hz), 4.12 (1H, dd, J = 5.0, 12.5 Hz), 3.53 (1H, dd, J = 3.9, 13.5 Hz), 3.47 (1H, dd, J = 5.3, 13.5 Hz), 2.13 (3H, s), 2.12 (3H, s), 2.07 (3H, s), 2.07 (3H, s), 2.07 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 170.0, 169.9, 169.8, 70.3, 68.6, 68.4,

68.4, 61.4, 50.6, 20.8, 20.8, 20.5. HRMS (EI) calcd.for $C_{16}H_{23}N_3NaO_{10}$ 440.1281, found 440.1271 $[M + Na]^+$.

Synthesis of 1-Azido-6-*O*-(*tert*-butyldiphenylsilyl)-1-deoxy-D-glucitol (21). Anhydrous K_2CO_3 (0.30 g, 2.21 mmol) was added to a stirred solution of pentaacetate **20** (3.69 g, 8.84 mmol) in MeOH (75 mL). Stirring was continued for 4 h at 25 °C, and the mixture was concentrated under reduced pressure. The residual traces of MeOH were removed by azeotropic evaporation with CH_3CN (3 × 20 mL). The residue was dissolved in pyridine (40 mL), and TBDPS-Cl (2.9 mL, 11.05 mmol) was added. The mixture was stirred for 33 h at 25 °C, and the solvent was removed by coevaporation with toluene (40 mL). The crude product was purified by flash column chromatography (CH_2Cl_2−MeOH 97/3) to afford compound **21** (3.72 g, 94%) as an oil: R_f 0.18 (CH_2Cl_2−MeOH 97/3); $[\alpha]^{20}_D$ −8.5 (*c* 1.09, $CHCl_3$); IR (film) 3414, 2931, 2891, 2847, 2104, 1428, 1113 cm^{-1}; EI-MS (*m*/*z*) 57 (100), 77 (68), 139 (41), 163 (94), 199 (75), 223 (14); ^1H NMR (500 MHz, $CDCl_3$) δ 7.66 (4H, m), 7.45 (2H, m), 7.40 (4H, m), 3.93 (1H, m), 3.83 (4H, m), 3.74 (1H, m), 3.47 (1H, dd, J = 7.0, 12.6 Hz), 3.41 (1H, dd, J = 4.8, 12.6 Hz), 3.34 (2H, br s), 3.25 (1H, br s), 2.96 (1H, br s), 1.07 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.6, 132.6, 130.1, 128.0, 74.1, 72.9, 71.6, 69.8, 65.2, 53.6, 26.9, 19.3. HRMS (EI) calcd for $C_{22}H_{32}N_3O_5Si$ 446.2111, found 446.2103 $[M + H]^+$.

Synthesis of 1-Azido-6-*O*-(*tert*-butyldiphenylsilyl)-1-deoxy-2,3,4,5-tetra-*O*-methyl-D-glucitol (22). A solution of tetrol **21** (3.67 g, 8.23 mmol) in DMF (40 mL) was added to a suspension of NaH (1.67 g, 65.84 mmol) in DMF (40 mL) at 0 °C. MeI (10 mL, 160.6 mmol) was added, and the suspension was stirred for 16 h at 25 °C. The mixture was poured into H_2O (1000 mL) and extracted with toluene (3 × 300 mL). The combined organic fractions were washed with brine (500 mL) and dried over $MgSO_4$. The residue was chromatographed (cyclohexane−EtOAc 9/1) to furnish a mixture (2,84 g, 69%) of migration products. LC-MS indicated that the mixture contained 80% of the desired compound **22** (2.27 g, 55%): R_f 0.19 (cyclohexane−EtOAc 9/1); $[\alpha]^{20}_D$ +1.0 (*c* 1.06, $CHCl_3$); IR (film) 2932, 2899, 2856, 2834, 2823, 2099, 1428, 1115, 1098 cm^{-1}; EI-MS (*m*/*z*) 45 (100), 101 (53), 135 (41), 167 (56), 213 (78), 384 (12), 444 (1); ^1H NMR (500 MHz, $CDCl_3$) δ 7.70 (4H, m), 7.40 (6H, m), 3.91 (1H, dd, J = 2.8, 11.4 Hz), 3.78 (1H, dd, J = 4.1, 11.4 Hz), 3.59 (1H, ddd, J = 3.4, 6.1, 7.5 Hz), 3.56 (1H, dd, J = 3.0, 7.2 Hz), 3.53 (1H, dd, J = 3.0, 6.1 Hz), 3.51 (3H, s), 3.48 (3H, s), 3.46 (1H, dd, J = 3.4, 13.1 Hz), 3.44 (3H, s), 3.38 (1H, dd, J = 7.5, 13.1 Hz), 3.30 (1H, ddd, J = 2.8, 4.1, 7.2 Hz), 1.07 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 136.5, 134.4, 134.2, 130.5, 128.6, 128.5, 82.2, 81.7, 80.9, 79.4, 62.4, 61.2, 60.8, 59.8, 58.6, 52.7, 27.8, 20.2. HRMS (EI) calcd for $C_{26}H_{40}N_3O_5Si$ 502.2737, found 502.2728 $[M + H]^+$.

Synthesis of 1-Azido-1-deoxy-2,3,4,5-tetra-*O*-methyl-D-glucitol (23). A solution of pure **22** (6.58 g, 13.11 mmol) and TBAF (1M in THF; 19.7 mL, 19.7 mmol) in THF (100 mL) was stirred at 25 °C for 14 h. The mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography (Et_2O) to afford alcohol **23** (3.43 g, 99%) as a pale yellow oil: R_f 0.32 (Et_2O); $[\alpha]^{20}_D$ +20.3 (*c* 1.07, $CHCl_3$); IR (film) 2936, 2831, 2100, 1092 cm^{-1}; EI-MS (*m*/*z*) 45 (100), 75 (55), 89 (40), 101 (55), 131 (25), 232 (1); ^1H NMR (500 MHz, $CDCl_3$) δ 3.90 (1H, br dt, J = 3.5, 12.1 Hz), 3.68 (1H, br ddd, J = 3.4, 7.6, 12.1 Hz), 3.60 (1H, ddd, J = 3.4, 5.8, 7.2 Hz), 3.52 (3H, s), 3.51 (3H, s), 3.48 (3H, s), 3.48 (3H, m), 3.43 (3H, s), 3.38 (1H, dd, J = 7.2, 13.1), 3.36 (1H, m), 2.15 (1H, br t, J = 4.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 81.7, 81.6, 81.1, 79.5, 61.3, 61.1, 60.2, 59.8, 58.2, 52.4. HRMS (EI) calcd for $C_{10}H_{22}N_3O_5$ 264.1559, found 264.1552 $[M + H]^+$.

Synthesis of 6-*O*-Allyl-1-azido-1-deoxy-2,3,4,5-tetra-*O*-methyl-D-glucitol (24). NaH (0.220 g, 8.74 mmol) and allyl bromide (756 μL, 8.74 mmol) were added consecutively to a stirred solution of alcohol **23** (1.15 g, 4.37 mmol) in DMF (20 mL) at 0 °C. The mixture was allowed to stir for 4 h at 25 °C before it was poured into H_2O (200 mL) and extracted with toluene (3 × 100 mL). The combined organic fractions were washed with brine (100 mL) and dried over $MgSO_4$. The residue was purified by chromatography (cyclohexane−EtOAc: 8/2) to yield allyl ether **24** (1.26 g, 95%) as an oil: R_f 0.22 (cyclohexane−EtOAc 8/2); $[\alpha]^{20}_D$ +6.8 (*c* 1.13, $CHCl_3$); IR (film) 2932, 2831, 2100, 1096 cm^{-1}; EI-MS (*m*/*z*) 41 (85), 45 (100), 71 (47), 101 (53); ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (1H, ddt, J = 5.7, 10.4, 17.2 Hz), 5.28 (1H, dd, J = 0.8, 17.2 Hz), 5.19 (1H, dd, J = 0.8, 10.4 Hz), 4.03 (2H, br d, J = 5.7 Hz), 3.76 (1H, dd, J = 2.9, 10.6) Hz, 3.60 (1H, ddd, J = 3.4, 6.0, 7.5 Hz), 3.51 (6H, s), 3.40−3.54 (5H, m), 3.44 (3H, s), 3.43 (3H, s), 3.37 (1H, dd, J = 7.5, 13.1); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.5, 117.2, 80.7, 79.9, 79.7, 78.7, 72.2, 67.2, 60.3, 59.9, 58.9, 57.3, 51.5. HRMS (EI) calcd for $C_{13}H_{26}N_3O_5$ 304.1872, found 304.1863 $[M + H]^+$.

Synthesis of 6-*O*-Allyl-1-amino-1-deoxy-2,3,4,5-tetra-*O*-methyl-D-glucitol (5). A solution of azide **24** (1.35 g, 4.47 mmol) in THF (20 mL) was added to a suspension of $LiAlH_4$ (0.255 g, 6.70 mmol) in THF (20 mL) at 0 °C. The reaction mixture was stirred for 5 h at 0 °C. *Carefully*, wet Et_2O (255 μL), a 15% NaOH solution (255 μL), and H_2O (765 μL), were added consecutively and the mixture was allowed to warm to 25 °C. The precipitate was removed by filtration through a cotton plug and washed with THF (200 mL). The filtrate was concentrated under reduced pressure, and a solution of the residue in CH_2Cl_2 (45 mL) was treated with Et_2O, saturated with HCl (5 mL). The solvent was removed under reduced pressure, and the residue was chromatographed (CH_2Cl_2−MeOH 7/1) to afford side chain **5** (1.31 g, 93%), which solidified very slowly upon standing: R_f 0.24 (CH_2Cl_2−MeOH 7/1); mp 61−63 °C; $[\alpha]^{20}_D$ −25.6 (*c* 1.07, $CHCl_3$); IR (film) 2984, 2936, 2835, 1094 cm^{-1}; EI-MS (*m*/*z*) 41 (28), 45 (24), 71 (13), 101 (100), 247 (<1), 278 (<1, M^+); ^1H NMR (500 MHz, $CDCl_3$) δ 5.92 (1H, ddt, J = 5.7, 10.4, 17.2 Hz), 5.28 (1H, ddd, J = 1.5, 3.1, 17.2 Hz), 5.18 (1H, dd, J = 1.5, 10.4 Hz), 4.03 (1H, dt, J = 1.2, 5.7 Hz), 3.90 (1H, ddd, J = 4.2, 5.7, 8.2 Hz), 3.75 (1H, dd, J = 2.9, 10.6 Hz), 3.64 (1H, dd, J = 2.3, 5.9 Hz), 3.48−3.55 (2H, m), 3.53 (3H, s), 3.52 (3H, s), 3.44 (1H, m), 3.44 (3H, s), 3.43 (3H, s), 3.30 (1H, dd, J = 4.2, 13.2 Hz), 3.10 (1H, dd, J = 8.2, 13.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.4, 118.2, 80.5, 80.4, 79.0, 77.4, 73.2, 68.1, 60.9, 60.6, 59.9, 58.4, 41.2. Anal. Calcd for $C_{13}H_{28}ClNO_5$: C, 49.75; H, 8.99; N, 4.46. Found: C, 48.28; H, 9.25; N, 4.31.

Synthesis of Compound 25. DMAP (291 mg, 2.38 mmol) and DSC (1.83 g, 7.14 mmol) were added to a stirred solution of alcohol **3** (734 mg, 2.38 mmol) in DMF (11.9 mL), and the mixture was stirred for 27 h at 25 °C. Then, it was poured into H_2O (250 mL) and extracted with Et_2O (3 × 250 mL). The combined organic fractions were washed with brine (250 mL) and dried over $MgSO_4$. The residue was treated with Et_2O, and the precipitate was filtered off. The filtrate was concentrated under reduced pressure, and the crude product was purified by flash column chromatography (*n*-pentane−acetone 75/25) to yield **25** (997 mg, 93%) as an oil: R_f 0.28 (*n*-pentane−acetone 75/25); $[\alpha]^{20}_D$ +20.3 (*c* 1.07, $CHCl_3$); IR (film) 1819, 1790, 1743, 1260, 1233, 1200, 1152, 1070, 1045 cm^{-1}; EI-MS (*m*/*z*) 41 (29), 88 (35), 121 (100), 449 (<1, M^+); ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.42 (5H, m), 5.88 (1H, ddt, J = 5.7, 10.4, 17.2 Hz), 5.26 (1H, ddd, J = 1.6, 3.1, 17.2 Hz), 5.18 (1H, dd, J = 1.4, 10.4 Hz), 4.97 (1H, t, J = 9.7 Hz), 4.15 (1H, d, J = 9.5 Hz), 4.06 (1H, ddt, J = 1.2, 5.7, 12.9 Hz), 3.99 (1H, ddt, J = 1.2, 5.7, 12.9 Hz), 3.73 (1H, ddd, J = 2.7, 4.5, 9.9 Hz), 3.67 (3H, s), 3.66 (1H, dd, J = 2.7, 11.0 Hz), 3.62 (1H, dd, J = 4.5, 11.0 Hz), 3.49 (1H, t, J = 9.1 Hz), 3.17 (1H, t, J = 9.2 Hz), 3.01 (3H, s), 2.84 (4H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 151.1, 138.3, 134.4, 128.2, 127.3, 117.4, 85.5, 85.5, 81.5, 78.4, 76.6, 72.6, 68.4, 61.2, 60.3, 25.4. HRMS (EI) calcd for $C_{22}H_{28}NO_9$ 450.1764, found 450.1754 $[M + H]^+$.

Synthesis of Compound 26. A solution of **25** (955 mg, 2.13 mmol) in THF (16 mL) was added to a stirred solution of side chain **5** (735 mg, 2.34 mmol), DMAP (26 mg, 0.213 mmol), and Et_3N (740 μL, 5.31 mmol) in THF (5 mL). The mixture was

stirred at 25 °C for 4 h, and the solvent was removed under reduced pressure. The residue was chromatographed (CH_2Cl_2−MeOH 97.5/2.5) to afford compound **26** (1.27 g, 98%) as a pale yellow oil: R_f 0.20 (CH_2Cl_2−MeOH 97.5/2.5); $[\alpha]^{20}_D$ −20.9 (*c* 1.00, $CHCl_3$); IR (film) 2976, 2934, 2899, 2832, 1728, 1531, 1245, 1098, 1066, 1028 cm^{-1}; EI-MS (*m*/*z*) 41 (89), 45 (89), 71 (44), 88 (91), 121 (100), 147 (11), 611 (<1, M^+); ^1H NMR (500 MHz, $CDCl_3$) δ 7.38 (2H, br d, J = 7.0 Hz), 7.33 (2H, br t, J = 7.0 Hz), 7.29 (1H, br t, J = 7.0 Hz), 5.93 (1H, ddt, J = 5.7, 10.9, 16.2 Hz), 5.84 (1H, ddt, J = 5.7, 10.9, 16.2 Hz), 5.28 (1H, dd, J = 1.2, 17.1 Hz), 5.26 (1H, m), 5.22 (1H, dd, J = 1.4, 17.1 Hz), 5.19 (1H, br d, J = 9.6 Hz), 5.12 (1H, dd, J = 1.2, 10.4 Hz), 4.78 (1H, t, J = 9.7 Hz), 4.13 (1H, d, J = 9.5 Hz), 4.04 (2H, br d, J = 5.7 Hz), 3.98 (2H, m), 3.77 (1H, dd, J = 2.7, 10.6 Hz), 3.69 (1H, ddd, J = 4.5, 7.2, 13.9 Hz), 3.64 (1H, ddd, J = 2.7, 6.3, 9.4 Hz), 3.42−3.52 (7H, m), 3.57 (3H, s), 3.54 (3H, s), 3.50 (3H, s), 3.49 (3H, s), 3.43 (3H, s), 3.36 (1H, t, J = 9.2 Hz), 3.13 (1H, t, J = 8.8 Hz), 3.12 (1H, m), 2.98 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 139.0, 134.7, 128.2, 128.1, 127.5, 117.3, 117.1, 86.0, 85.7, 81.6, 81.3, 79.9, 79.7, 79.1, 78.2, 72.6, 72.4, 72.1, 70.1, 67.5, 60.6, 60.6, 60.3, 59.2, 57.5, 41.8. Anal. Calcd for $C_{31}H_{49}NO_{11}$: C, 60.87; H, 8.07; N, 2.29. Found: C, 60.85; H, 8.18; N, 2.34.

Synthesis of Compound 1. A solution of diene **26** (1.25 g, 2.05 mmol) in dry and degassed CH_2Cl_2 (25 mL) and a solution of Grubbs' first generation catalyst (170 mg, 0.205 mmol) in dry and degassed CH_2Cl_2 (10 mL) were added slowly and simultaneously to stirred dry and degassed CH_2Cl_2 (375 mL) over a period of 2 h at 25 °C. The solution was allowed to stir for 3 additional hours and, then, a fresh solution of Grubbs' first generation catalyst (85 mg, 0.103 mmol) in dry and degassed CH_2Cl_2 (10 mL) was added slowly. The mixture was stirred for another 24 h, and the reaction was quenched by addition of DMSO (1.1 mL, 15.4 mmol). The mixture was exposed to air and stirred for 24 h. The solvent was removed under reduced pressure, and the dark brown residue was chromatographed (cyclohexane−acetone 7/3) to yield a mixture of *E*-isomer **1a** and *Z*-isomer **1b** (1.132 g, 94%). Chromatography on $AgNO_3$-impregnated silica gel (CH_2Cl_2−MeOH 96.5/3.5) followed by filtration over silica gel to remove traces of $AgNO_3$ afforded pure **1a** (891 mg, 74%) as white crystals and pure **1b** (240 mg, 20%) as a foam. Data for **1a**: R_f 0.28 (CH_2Cl_2−MeOH 96.5/3.5), R_f ($AgNO_3$) 0.30 (CH_2Cl_2−MeOH 96/4); mp 148−150 °C; $[\alpha]^{20}_D$ +30.8 (*c* 1.02, $CHCl_3$); IR (film) 2976, 2934, 2899, 2856, 2834, 1720, 1703, 1523, 1508, 1458, 1371, 1248, 1142, 1085, 1066, 1028 cm^{-1}; EI-MS (*m*/*z*) 41 (38), 45 (92), 71 (73), 88 (75), 101 (100), 134 (40), 147 (15), 187 (22), 552 (3), 583 (<1, M^+); ES-MS (*m*/*z*) 584 $[M + H]^+$, 606 $[M + Na]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (2H, br d, J = 7.2 Hz), 7.33 (2H, br t, J = 7.2 Hz), 7.29 (1H, br t, J = 7.2 Hz), 5.72 (1H, dt, J = 4.8, 15.9 Hz), 5.67 (1H, dt, J = 5.1, 15.9 Hz), 4.82 (1H, m), 4.79 (1H, t, J = 9.7 Hz), 4.13 (1H, d, J = 9.5 Hz), 4.05 (2H, m), 3.92 (2H, m), 3.83 (1H, dd, J = 2.3, 6.7 Hz), 3.81 (1H, ddd, J = 3.1, 8.2, 12.4 Hz), 3.72 (1H, dd, J = 5.7, 9.8 Hz), 3.55−3.65 (2H, m), 3.59 (3H, s), 3.57 (3H, s), 3.56 (3H, s), 3.43−3.52 (3H, m), 3.46 (3H, s), 3.45 (3H, s), 3.41 (1H, dd, J = 4.2, 6.8 Hz), 3.39 (1H, m), 3.35 (1H, t, J = 9.2 Hz), 3.23 (1H, ddd, J = 3.6, 8.2, 12.6 Hz), 3.16 (1H, t, J = 9.2 Hz), 2.99 (3H, s); ^1H NMR (500 MHz, C_6D_6) δ 7.42 (2H, br d, J = 7.2 Hz), 7.15 (2H, m), 7.10 (1H, br t, J = 7.2 Hz), 5.66 (1H, dt, J = 5.5, 15.6 Hz), 5.56 (1H, dt, J = 5.0, 15.6 Hz), 5.37 (1H, t, J = 9.5 Hz), 4.73 (1H, dd, J = 3.7, 7.9 Hz), 4.14 (1H, d, J = 9.5 Hz), 4.06 (1H, dd, J = 2.4, 6.9 Hz), 3.95 (1H, ddd, J = 3.5, 8.3, 12.5 Hz), 3.88 (1H, dd, J = 6.5, 9.5 Hz), 3.85 (2H, br d, J = 5.1 Hz), 3.79 (1H, m), 3.74 (2H, br d, J = 3.9 Hz), 3.67 (1H, m), 3.66 (1H, t, J = 8.1 Hz), 3.61 (1H, m), 3.54 (3H, s), 3.52 (1H, m), 3.51 (3H, s), 3.47 (1H, m), 3.45 (3H, s), 3.43 (1H, t, J = 9.3 Hz), 3.23 (3H, s), 3.19 (1H, ddd, J = 3.6, 8.2, 12.6 Hz), 3.15 (1H, t, J = 9.2 Hz), 3.08 (3H, s), 2.88 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.8, 138.7, 129.9, 128.7, 128.2, 128.0, 127.5, 85.7, 85.5, 81.4, 80.2, 79.9, 79.3, 77.1, 72.2, 71.4, 70.6, 69.0, 68.4, 60.5, 60.4, 60.1, 57.6, 57.5, 39.1. Anal. Calcd for $C_{29}H_{45}NO_{11}$: C, 59.67; H, 7.77; N, 2.40. Found: C, 59.71; H, 7.73; N, 2.49. Data for **1b**: R_f 0.28 (CH_2Cl_2−MeOH 96.5/3.5), R_f ($AgNO_3$) 0.18 (CH_2Cl_2−MeOH 96/4); $[\alpha]^{20}_D$ +38.7 (*c* 1.03, $CHCl_3$); IR (film) 2932, 2899, 1724, 1243, 1142, 1095, 1066 cm^{-1}; EI-MS (*m*/*z*) 41 (35), 45 (85), 71 (68), 88 (70), 101 (100), 134 (37), 147 (14), 187 (20), 552 (2), 583 (<1, M^+); ES-MS (*m*/*z*) 584 $[M + H]^+$, 606 $[M + Na]^+$; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39 (2H, br d, J = 7.2 Hz), 7.32 (2H, br t, J = 7.2 Hz), 7.27 (1H, br t, J = 7.2 Hz), 5.70 (1H, dt, J = 5.0, 11.5 Hz), 5.67 (1H, dt, J = 5.4, 11.5 Hz), 4.94 (1H, dd, J = 2.6, 8.3 Hz), 4.85 (1H, t, J = 9.5 Hz), 4.25 (1H, dd, J = 5.4, 12.8 Hz), 4.12 (1H, d, J = 9.4 Hz), 4.10 (1H, dd, J = 3.9, 12.8 Hz), 4.06 (2H, m), 3.71 (1H, ddd, J = 2.5, 8.4, 14.0 Hz), 3.66 (1H, dd, J = 3.9, 10.9 Hz), 3.63 (1H, t, J = 4.9 Hz), 3.50−3.60 (4H, m), 3.57 (3H, s), 3.56 (3H, s), 3.52 (3H, s), 3.48 (3H, s), 3.46 (2H, m), 3.42 (3H, s), 3.38 (1H, m), 3.35 (1H, t, J = 9.3 Hz), 3.29 (1H, ddd, J = 3.2, 5.6, 13.9 Hz), 3.16 (1H, t, J = 9.2 Hz), 2.98 (3H, s); ^1H NMR (500 MHz, C_6D_6) δ 7.44 (2H, br d, J = 7.2 Hz), 7.15 (2H, m), 7.10 (1H, br t, J = 7.2 Hz), 5.79 (1H, p, J = 5.4 Hz), 5.51 (1H, p, J = 5.6 Hz), 5.46 (1H, t, J = 9.8 Hz), 4.77 (1H, br d, J = 7.1 Hz), 4.51 (1H, br dd, J = 6.8, 13.4 Hz), 4.18 (1H, br dd, J = 4.6, 13.4 Hz), 4.13 (1H, d, J = 9.5 Hz), 3.90 (1H, br dd, J = 5.2, 12.6 Hz), 3.78−3.87 (3H, m), 3.76 (1H, dd, J = 2.3, 10.9 Hz), 3.68−3.74 (2H, m), 3.52−3.59 (4H, m), 3.54 (3H, s), 3.49 (3H, s), 3.47 (1H, m), 3.47 (3H, s), 3.41 (1H, t, J = 9.2 Hz), 3.14 (3H, s), 3.13 (1H, m), 3.13 (3H, s), 3.09 (1H, ddd, J = 2.3, 4.9, 14.3 Hz), 2.86 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 138.8, 130.2, 128.4, 128.1, 128.0, 127.5, 85.7, 85.6, 81.5, 80.7, 80.6, 80.2, 80.0, 78.1, 71.6, 68.8, 67.3, 67.3, 61.0, 60.5, 60.3, 60.1, 57.9, 57.0, 39.6. Anal. Calcd for $C_{29}H_{45}NO_{11}$: C, 59.67; H, 7.77; N, 2.40. Found: C, 59.67; H, 7.72; N, 2.29.

Synthesis of Compound 27a. NaH (60% dispersion in mineral oil; 7 mg, 0.172 mmol) was added to a stirred solution of **1a** (52 mg, 0.089 mmol) in DMF (860 μL) at 0 °C. After 5 min, MeI (27 μL, 0.430 mmol) was added, and the mixture was stirred for an additional 90 min at 0 °C. The mixture was poured into H_2O (25 mL) and extracted with Et_2O (3 × 25 mL). The combined organic fractions were washed with brine (25 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was chromatographed (*n*-hexane−acetone 75/25) to yield compound **27a** (53 mg, 99%) as a white foam: R_f 0.24 (*n*-hexane−acetone 75/25); $[\alpha]^{20}_D$ +24.8 (*c* 1.00, $CHCl_3$); IR (film) 2934, 2899, 2834, 1704, 1103, 1090 cm^{-1}; EI-MS (*m*/*z*) 88 (83), 101 (100), 187 (23), 201 (8), 566 (3), 597 (<1, M^+); ES-MS (*m*/*z*) 598 $[M + H]^+$; ^1H NMR (500 MHz, DMSO-d_6) δ 4.71 (1H, t, J = 9.5 Hz, H4 minor rotamer), 4.59 (1H, t, J = 9.7 Hz, H4 major rotamer); ^{13}C NMR (125 MHz, DMSO-d_6) see the Supporting Information. HRMS (EI) calcd for $C_{30}H_{48}NO_{11}$ 598.3227, found 598.3213 $[M + H]^+$.

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Supporting Information Available: Synthesis and spectroscopic data of compounds **2a**, **2b**, **13**, **14**, **15**, **16**, **17b**, **18a**, and **18b**; ^1H and ^{13}C NMR spectra of all new compounds; preparation of Raney nickel W4; preparation of $AgNO_3$-impregnated silica gel and TLC plates; full experimental details on screening protocols and biological activities of macrolide analogues **1a**, **1b**, **2a**, and **2b**; and a detailed description of the calculation of the free energy of activation for rotation including details of the ^1H NMR spectra recorded at elevated temperatures. This material is available free of charge via the Internet at http://pubs.acs.org.

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