JOC Article

The Use of a Mannitol-Derived Fused Oxacycle as a Combinatorial Scaffold

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An efficient and high-yielding solid-phase synthesis of a small library of compounds containing a cis-fused pyranofuran structural motive is descibed. With use of the cheap and readily available D-(+)-mannitol, a highly functionalized sugar template was synthesized and immobilized on a solid support via an olefinic linker. Modification of this two-point molecular scaffold and subsequent ring-closing metathesis/cleavage gave access to a series of functionalized conformationally constrained fused oxacycles.

Introduction

Over the past decade several groups have reported the synthesis of combinatorial scaffolds starting from naturally occurring compounds, such as peptides,[1] steroids,[2] and carbohydrates.[3] The molecular framework and the high density of functionalities of these scaffolds allows the incorporation and spatial arrangement of pharmacophoric groups. In 1993, Hirschmann et al. revealed for the first time that β-D-glucose could be used as a scaffolding for peptidomimetics.[3a] Later on several other groups described the transformation of glycosides into orthogonally protected building blocks and their usefulness in setting up a combinatorial library.[3b−i] A potential disadvantage in the application of monosaccharide scaffolds may be their propensity, depending on the nature and spatial orientation of the substituents, to adopt more than one conformation (i.e. chair and boat conformations). We envisaged that generation of carbohydrate-based fused oxacycles would lead to scaffolds featuring enhanced conformational constraints, while still endowed with functionalities suitable for combinatorial elaboration. In this respect, we have shown that the introduction of a bis terminal diene on a sugar-template (C, Scheme 1) allows ruthenium-alkylidene **A** catalyzed ring-closing metathesis (RCM) to form fused oxacycles (**D**).[4,5] Replacement of one of the terminal alkenes by an olefinic linker (**E**) would allow attachment to a solid support. Subsequent introduction of pharmacophoric groups (**F**), followed by a ring-closing metathesis cyclization/cleavage procedure[6] with the more powerful second generation Grubbs catalyst **B**,[7] would lead to functionalized fused oxacycles (**G**).

We here report the design and synthesis of a highly functionalized sugar template and its use in the construction of a small combinatorial library containing the conformationally constrained pyranofuran structural motive.

Results and Discussion

The construction of the target combinatorial library comprises the immobilization of a highly functionalized sugar diene, the introduction of pharmacophoric groups,

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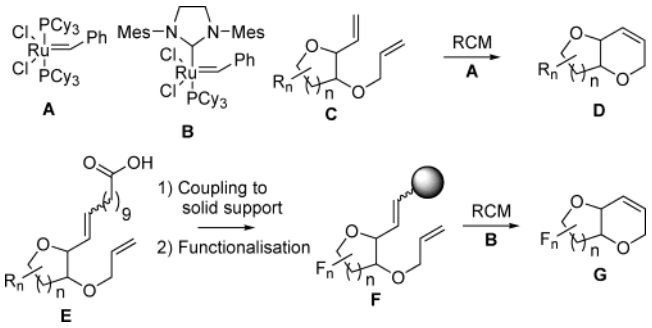
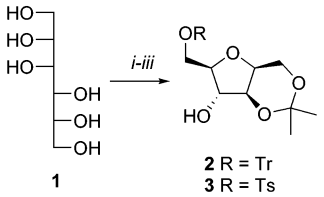
SCHEME 1. Ring-Closing Metathesis Cyclization/ Cleavage



SCHEME 2. Preparation 2,5-Anhydro-D-glucitol[a]



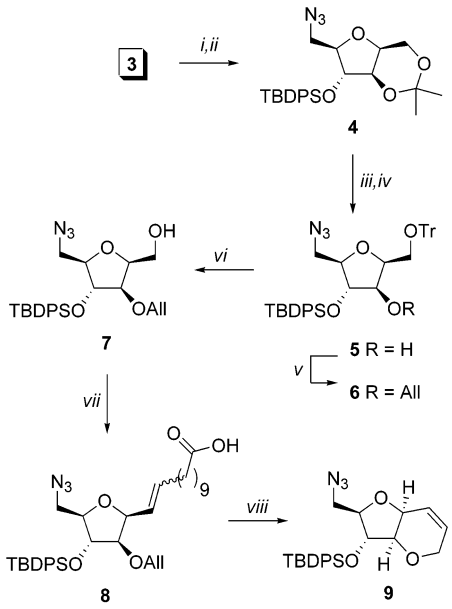
[a] Reagents and conditions: (i) conc aq HCl, reflux, 48 h; (ii) 2-methoxypropene, acetone, 24 h; (iii) TsCl, pyridine, 24 h, 21% (R = Ts).

and its release from the solid support. The first stage requires the large-scale synthesis of a sugar-derived diene template that will be amenable for coupling on a solid support. It occurred to us that trityl-protected 2,5-anhydroglucitol derivative **2**,[8] obtained from cheap and readily available D-(+)-mannitol (Scheme 2), would in principle be a suitable starting compound for the synthesis of diene **8** (Scheme 3). Unfortunately, the removal of the trityl protecting group in **2** (Scheme 2), using either acidic or hydrogenating conditions, was not fully compatible with the isopropylidene group. The latter disadvantage was an incentive to substitute the trityl group by a tosyl group, which can be readily replaced by other functional groups.

The synthesis of tosylate **3**, earlier reported by Koell et al.,[9] was readily accomplished by the following sequential three-step procedure. Acidic dehydration of D-(+)-mannitol (**1**) at elevated temperature went to completion, as gauged by ^{13}C NMR, to give a mixture of anhydrides. Acetonation of the latter mixture following the original procedure was not satisfactory. On the other hand, acetonation in the presence of 2-methoxypropene proceeded smoothly. Flash-column chromatography yielded an inseparable mixture of the desired 1,3-*O*-isopropylidine-2,5-anhydro-D-glucitol (**2**, R = H) and 1,4:3,6-dianhydro-D-mannitol (isomannide). Subsequent treatment of this mixture with tosyl chloride in pyridine gave, after selective crystallization, tosylate **3** in an overall yield of 21%.

The 4- and 6-positions in **3** were now selected for the introduction of pharmacophoric groups, leaving the 1- and 3-positions for the installation of the diene. Thus, treatment of tosylate **3** (Scheme 3) with sodium azide and a catalytic amount of tetra-*n*-butylammonium iodide

SCHEME 3. Synthesis and RCM of the Orthogonally Protected Template 8[a]



[a] Reagents and conditions: (i) NaN_3, TBAI (cat.), DMF, 80 °C, 16 h; (ii) TBDPSCl (1.1 equiv), imidazole (2 equiv), DMF, 16 h, 85% (2 steps); (iii) TFA/MeOH/DCM, 5/60/35, v/v/v, 3 h, quantitative; (iv) trityl chloride (1.1 equiv), pyridine, 16 h; (v) allyl bromide (2 equiv), KHMDS (1.1 equiv), DMF, 1 h; (vi) TiPSH (1.5 equiv), TFA (1.5 equiv), DCM, 15 min, 72% (3 steps); (vii) (a) Dess−Martin periodinane (1.2 equiv), DCM, 1 h; (b) $BrPh_3P(CH_2)_{10}COOH$ (1.2 equiv), KHMDS (2.4 equiv), THF, −78 °C, 1 h, then **5**, −78 → −20 °C, 2 h, 80% (2 steps); (viii) **B** (0.01 equiv), DCM, reflux, 1 h, 99%.

(TBAI) in DMF at elevated temperature, followed by silylation of the crude azide with TBDPSCl, gave the fully protected anhydroglucitol **4** in 85% yield over the two steps.

Transformation of **4** into the required diene **8** entailed the following five-step procedure. Removal of the isopropylidene protecting group in **4** by acid-mediated methanolysis and subsequent tritylation of the primary hydroxyl gave compound **5**. Allylation of the free secondary hydroxyl in **5** with allyl bromide under the agency of potassium hexamethyldisilazane (KHMDS) in DMF furnished allyl ether **6**. Mild acidic cleavage of the trityl protecting group in the presence of the cation scavenger triisopropylsilane (TiPSH) gave, after purification, homogeneous **7**. Dess−Martin oxidation of the primary alcohol in **7** and subsequent Wittig olefination resulted in an E/Z mixture of target diene **8** in 58% yield over the five steps. In view of the intended cyclization of **13** into **14** (Scheme 4) it was gratifying to establish that subjection of **8** to the second generation Grubbs catalyst **B** (1 mol %) in refluxing dichloromethane led to the isolation of the ring-closed product pyranofuran **9** in a near-quantitative yield.

At this stage, the potential usefulness of **9** as a scaffold was explored. To this end, compound **8** was desilylated[10] (Scheme 4) with tetra-*n*-butylammonium fluoride (TBAF) in THF to afford **10**, which was coupled to Rink-amide resin with use of the condensating agent BOP in the presence of DiPEA.

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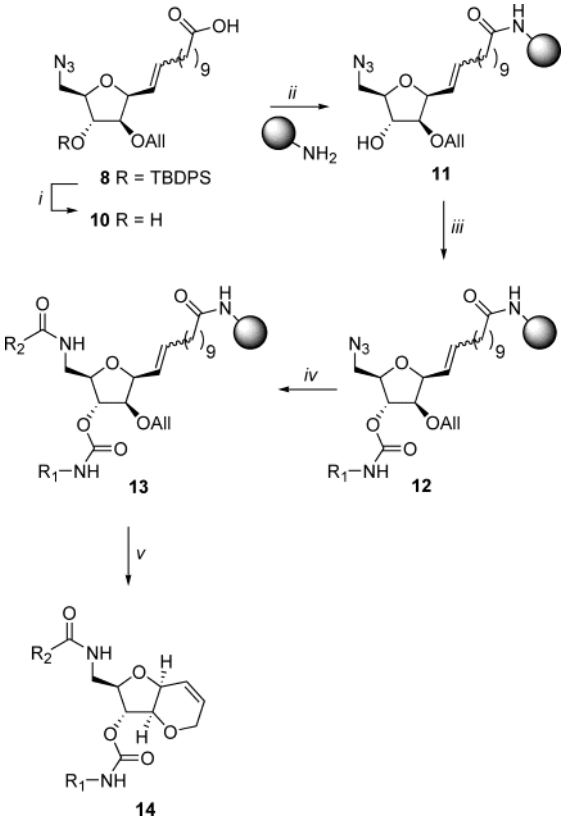
(10) Removal of the TBDPS group on solid support resulted in lower yields and purities of cleaved products.

SCHEME 4. Solid-Phase Functionalization and Ring-Closing Metathesis[a]



[a] Reagents and conditions: (i) TBAF, THF, 1 h, 89%; (ii) BOP, DiPEA, 16 h; (iii) $R_1-N=C=O$ (R_1 = Bn, MeOPh, or Ph), TEA, 16 h; (iv) (a) Me_3P, THF, 1 h, then H_2O/dioxane, 2 h; (b) $R_2-C(O)Cl$ (R_2 = Ph_2N, BnO, or Ph), DiPEA, 16 h; (v) **B** (5 mol %), DCM, reflux, 16 h, for yields see Table 1.

The parallel synthesis of a nine-membered compound library commences, as depicted in Scheme 4, with the condensation of **11** with either benzyl-, methoxyphenyl-, or phenyl isocyanate to give carbamates **12**. Subsequent Staudinger reduction of the individual azides **12** and condensation of the free amines with diphenylcarbamoyl, benzyloxycarbonyl or benzoyl chloride gave the fully functionalized resins **13**. Cyclization/cleavage of these resins was effected with 5 mol % of Grubbs catalyst **B** in refluxing dichloromethane for 16 h and gave the released pyranofurans **14**. Purification of the latter compounds by flash column chromatography over a silica-plug gave the homogeneous products in good to excellent yields (Table 1), indicating that both the functionalization and cleavage steps were near quantitative.

In conclusion, we have reported a robust and high-yielding synthesis of a novel sugar-derived scaffold and its efficient on-resin functionalization, with concomitant cyclization/cleavage to give access to a 3 × 3 library of pyranofurans. The scope of our strategy for the construction of rigid scaffolds with different ring-sizes and substitution patterns is currently under investigation.

Experimental Section

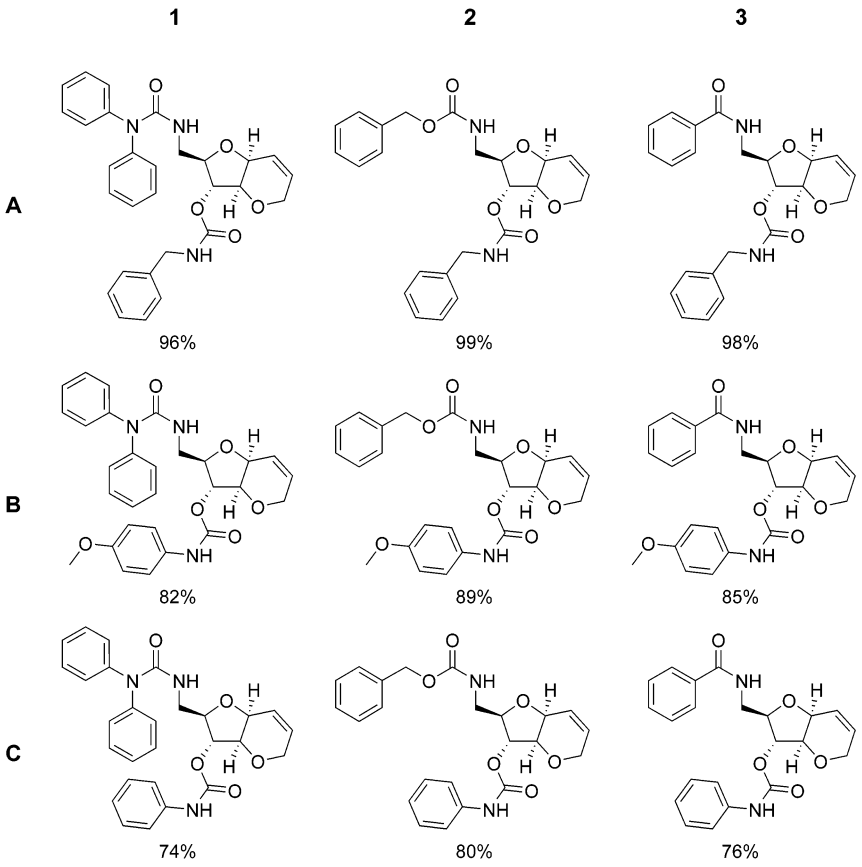
2,5-Anhydro-1,3-*O*-isopropylidene-6-*O*-tosyl-D-glucitol (3). A suspension of D-mannitol (182 g, 1 mol) in saturated aqueous HCl (0.75 L) was refluxed for 48 h. After concentration of the reaction mixture, acetone (1 L) and 2-methoxypropene (75 mL) were added and the mixture was allowed to stir overnight. Triethylamine (50 mL) was added and the mixture was concentrated in vacuo. Flash-column chromatography (toluene/ethyl acetate, 1/1, v/v) yielded a mixture of 2,5-anhydro-1,3-*O*-isopropylidene-D-glucitol and isomannide, which was treated with tosyl chloride (76.3 g, 400 mmol) in pyridine (500 mL) for 16 h. After concentration of the reaction mixture, the residue was taken up in ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and evaporated. Crystallization of the crude product (toluene/light petroleum ether) yielded the title compound as white crystals (74.9 g, 209 mmol, 21%). Mp 96−98 °C; $[\alpha]^{20}_D$ +14.2 (*c* 1.0, $CHCl_3$); IR (thin film) 3429, 2989, 2935, 1597, 1354, 1173, 1099 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 8.2 Hz, 2H), 7.34 (d, J = 8.2 Hz, 2H), 4.18−3.89 (m, 8H), 2.44 (s, 3H), 1.93 (br s, 1H), 1.38 (s, 3H), 1.23 (s, 3H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 144.9, 132.5, 129.9, 128.1, 97.3, 83.6, 78.0, 75.5, 73.0, 69.9, 60.3, 28.7, 22.5, 18.7; HRMS *m*/*z* calcd for $C_{16}H_{22}O_7SH$ 359.1164, obsd 359.1161.

2,5-Anhydro-6-azido-4-*O*-*tert*-butyldiphenylsilanyl-6-deoxy-1,3-*O*-isopropylidene-D-glucitol (4). Tosylate **3** (29.7 g, 83 mmol) was coevaportated with DMF and dissolved in DMF (200 mL). After addition of NaN_3 (5 equiv, 415 mmol, 27.0 g) the reaction mixture was stirred at 80 °C for 16 h. After concentration of the reaction mixture, the residue was taken up in ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and evaporated. The residue was coevaporated with DMF, dissolved in DMF (200 mL), and treated with TBDPSCl (100 mmol, 27 mL) and imidazole (100 mmol, 6.8 g). After the mixture was stirred overnight at room temperature the solvent was removed in vacuo and the residue was taken up in ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (toluene) to give homogeneous **4** (33 g, 71 mmol, 85%) as a colorless oil. $[\alpha]^{20}_D$ +5.0 (*c* 0.1, CH_3CN); IR (thin film) 2931, 2858, 2098, 1470, 1427, 1107 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.38 (m, 6H), 4.01 (m, 6H), 3.27 (dd, 1H, J = 8.0, 12.8 Hz), 2.83 (dd, 1H, J = 4.8, 12.8 Hz), 1.26 (s, 3H), 1.23 (s, 3H), 1.09 (s, 9H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 135.6, 132.9, 132.7, 129.9, 127.7, 97.1, 85.9, 80.1, 75.8, 73.1, 60.4, 52.4, 28.5, 26.7, 18.8, 18.7; HRMS *m*/*z* calcd for $C_{25}H_{33}N_3O_4SiNa$ 490.2138, obsd 490.2143.

2,5-Anhydro-6-azido-4-*O*-*tert*-butyldiphenylsilanyl-6-deoxy-D-glucitol. Glucitol **4** (20 g, 43 mmol) was dissolved in MeOH/DCM (200 mL, 3/1, v/v) and trifluoroacetic acid (10 mL) was added. After standing for 3 h, the reaction mixture was neutralized with triethylamine, concentrated in vacuo, and coevaporated with toluene. The residue was used without further purification. ^1H NMR (200 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.38 (m, 6H), 4.23−3.93 (m, 4H), 3.98 (dd, 1H, J = 1.5, 2.6 Hz), 3.90 (ddd, 1H, J = 2.6, 3.3, 5.8 Hz), 3.04 (dd, 1H, J = 3.3, 12.8 Hz), 2.88 (dd, 1H, J = 5.8, 12.8 Hz), 1.08 (s, 9H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 135.5, 132.9, 132.7, 129.9, 127.7, 84.8, 80.8, 80.4, 78.9, 60.9, 52.1, 26.6, 18.8; ESI-MS (*m*/*e*) 450.1 [M + Na]$^+$, 855.5 [2M + H]$^+$, 877.5 [2M + Na]$^+$.

2,5-Anhydro-6-azido-4-*O*-*tert*-butyldiphenylsilanyl-6-deoxy-1-*O*-triphenylmethyl-D-glucitol (5). 2,5-Anhydro-6-azido-4-*O*-*tert*-butyldiphenylsilanyl-6-deoxy-D-glucitol (15.4 g, 36 mmol) was coevaporated with pyridine, dissolved in pyridine (200 mL), and treated with triphenylmethyl chloride (11 g, 40 mmol). After standing overnight, the reaction mixture was concentrated in vacuo and the residue was taken up in ethyl acetate, washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), filtered and concentrated. The residue was used without further purification. IR (thin film) 3456, 3066, 2931, 2858, 2098, 1489, 1447, 1427, 1277, 1111, 1061 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.65−7.16 (m, 25H), 4.24 (app dt, 1H, J = 3.3, 4.6 Hz), 4.08 (ddd, 1H, J = 1.1, 3.3, 5.4 Hz), 3.98 (dd, 1H, J = 1.1, 2.2 Hz), 3.94 (ddd, 1H, J = 2.2, 5.7, 4.0 Hz), 3.55 (dd, 1H, J = 4.6, 10.6 Hz), 3.48 (dd, 1H, J = 4.6,

TABLE 1. 3 × 3 Library of Pyranofurans 14



10.6 Hz), 3.09 (d, 1H, J = 5.4 Hz), 3.01 (dd, 1H, J = 5.7, 12.6 Hz), 2.92 (dd, 1H, J = 4.0, 12.6 Hz), 1.10 (s, 9H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 143.4, 135.7, 135.6, 130.1, 130.0, 130.1, 130.0, 128.5, 127.7, 127.1, 87.3, 85.4, 80.9, 80.2, 78.9, 62.5, 52.7, 26.8, 19.0; HRMS *m*/*z* calcd for $C_{41}H_{43}N_3O_4SiNa$ 692.2920, obsd 692.2993.

3-*O*-Allyl-2,5-anhydro-6-azido-4-*O*-*tert*-butyldiphenylsilanyl-6-deoxy-1-*O*-triphenylmethyl-D-glucitol (6). 2,5-Anhydro-6-azido-4-*O*-*tert*-butyldiphenylsilanyl-6-deoxy-D-glucitol (**5**) (10.2 g, 15 mmol) was coevaporated with DMF and dissolved in DMF (100 mL). Allyl bromide (30 mmol, 2.6 mL) was added and the mixture was cooled to 0 °C. After dropwise addition of KHMDS (16.5 mmol, 33 mL 0.5 M in toluene), the mixture was allowed to warm to room temperature. Water (100 mL) was added and the aqueous layer was extracted with ether (2 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated. The residue was purified by column chromatography (light petroleum ether/toluene, 100% → 75%, v/v) yielding the title compound (7.8 g, 10.8 mmol, 72%, 3 steps). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72−7.14 (m, 25H), 5.46 (app ddt, 1H, J = 10.7, 17.0, 5.3 Hz), 4.91 (app dq, 1H, J = 10.7, 1.4 Hz), 4.86 (app dq, 1H, J = 17.0, 1.4 Hz), 4.38 (ddd, 1H, J = 3.3, 5.8, 6.2 Hz), 4.05 (ddd, 1H, J = 1.6, 5.3, 7.3 Hz), 4.00 (dd, 1H, J = 0.9, 1.6 Hz), 3.66 (dd, 1H, J = 0.9, 3.2 Hz), 3.46 (ddt, 1H, J = 5.3, 16.3, 1.4 Hz), 3.46 (dd, 1H, J = 5.8, 9.6 Hz), 3.32 (ddt, 1H, J = 5.3, 16.3, 1.4 Hz), 3.05 (dd, 1H, J = 6.2, 9.6 Hz), 1.10 (s, 9H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 143.8, 135.6, 134.0, 132.9, 132.6, 129.9, 128.5, 127.7, 127.6, 116.2, 86.6, 85.5, 84.1, 80.5, 77.6, 70.0, 61.9, 52.3, 26.7, 18.8.

3-*O*-Allyl-2,5-anhydro-6-azido-4-*O*-*tert*-butyldiphenylsilanyl-6-deoxy-D-glucitol (7). 3-*O*-Allyl-2,5-anhydro-6-azido-4-*O*-*tert*-butyldiphenylsilanyl-6-deoxy-1-*O*-triphenylmethyl-D-glucitol (**6**) (0.72 g, 1.0 mmol) was coevaporated with toluene and dissolved in DCM (5 mL). After the addition of TiPSH (1.0 mmol, 0.22 mL), a solution of TFA (1.1 mmol, 0.090 mL) and TiPSH (1.0 mmol, 0.22 mL) in DCM (1.69 mL) was added dropwise. After 30 min, MeOH (1 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL) were added. The aqueous layer was extracted with DCM and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was purified by column chromatography (toluene → 5% ethyl acetate in toluene) to gain homogeneous **7** (0.48 g, 0.99 mmol, 99%). IR (thin film) 3456, 3066, 2928, 2858, 2098, 1489, 1447, 1427, 1277, 1107, 1076 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72−7.35 (m, 10H), 5.46 (ddt, 1H, J = 10.7, 17.0, 5.3 Hz), 5.06 (app dq, 1H, J = 17.0, 1.5 Hz), 5.05 (app dq, 1H, J = 10.7, 1.5 Hz), 4.31 (app q, 1H, J = 5.2 Hz), 4.11−4.03 (m, 2H), 3.86−3.82 (m, 2H), 3.76−3.81 (m, 2H), 3.76 (dd, 1H, J = 1.1, 3.7 Hz), 3.55 (app ddt, 1H, J = 5.3, 12.9, 1.5 Hz), 3.55 (app ddt, 1H, J = 5.3, 12.9, 1.5 Hz), 3.08 (dd, 1H, J = 6.8, 12.6 Hz), 2.96 (dd, 1H, J = 5.3, 12.6 Hz), 2.46 (br s, 1H), 1.10 (s, 9H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 135.7, 133.7, 132.8, 132.7, 130.1, 127.9, 116.9, 85.3, 81.1, 77.4, 70.1, 61.4, 52.2, 26.7, 18.9; HRMS *m*/*z* calcd for $C_{25}H_{33}N_3O_4SiNa$ 490.2138, obsd 490.2181.

***E*/*Z*-11-[(2*S*,3*R*,4*S*,5*R*)-3-Allyloxy-5-azidomethyl-4-*tert*-butyldiphenylsilanyloxytetrahydrofuran-2-yl]undec-10-enoic Acid (8).** Anhydroglucitol **7** (0.32 g, 0.68 mmol) was coevaporated with toluene and dissolved in DCM (5 mL) and Dess−Martin periodinane (0.44 g, 1.04 mmol) was added. After 1 h, DCM (15 mL), saturated aqueous $Na_2S_2O_3$ (14 mL), and saturated aqueous $NaHCO_3$ (6 mL) were added. After the solution was stirred for 30 min, the aqueous layer was extracted with DCM and the combined organic layers were dried ($MgSO_4$), filtered, and evaporated to gain the aldehyde. KHMDS (2.0 mmol, 4.0 mL 0.5 M in toluene) was added to a cooled (−78 °C) and stirred solution of (10-carboxydecyl)-triphenylphosphonium bromide[11] (1.0 mmol, 0.53 g) in dry THF. After the mixture was stirredg for 1 h, the aldehyde in

(11) Narayanan, K. S.; Berlin, K. D. *J. Org. Chem.* **1980**, *45*, 2240.

dry THF (2 mL) was added dropwise. After being stirred for 1 h, the reaction mixture was allowed to warm to rt. Saturated aq NH_4Cl was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered, and evaporated. Column chromatography of the crude product (toluene → 1% acetic acid in toluene) yielded pure **8** (0.36 g, 0.57 mmol, 84%). $[\alpha]^{20}_D$ +2.4 (*c* 0.1, MeCN); IR (thin film) 2928, 2855, 2098, 1709, 1489, 1452, 1427, 1277, 1107 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.72−7.35 (m, 10H), 5.51 (m, 3H), 5.05 (m, 3H), 4.02 (m, 2H), 3.49 (m, 3H), 3.14 (dd, 1H, J = 6.9, 12.4 Hz), 3.14 (dd, 1H, J = 5.9, 12.4 Hz), 2.35 (t, 2H, J = 7.3 Hz), 2.13 (m, 2H), 1.64 (m, 2H), 1.30 (m, 12H), 1.09 (s, 9H); ^{13}C NMR (50.1 MHz, $CDCl_3$) δ 179.5, 135.5, 134.3, 134.0, 132.9, 132.6, 129.9, 127.7, 124.6, 116.9, 85.8, 84.9, 78.2, 76.7, 70.0, 52.1, 33.8, 29.7, 29.1, 28.9, 28.8, 27.7, 26.6, 18.7; ESI-MS (*m*/*e*) 656.3 $[M + Na]^+$; HRMS *m*/*z* calcd for $C_{36}H_{51}N_3O_5SiNa$ 656.3495, obsd 656.3514.

(4a*S*,6*R*,7*R*,7a*S*)-6-Azidomethyl-7-*tert*-butyldiphenylsilanyloxy-1,5-dioxabicyclo[4.3.0]non-3-ene (9). Anhydroglucitol **8** (0.20 g, 0.32 mmol) was coevaporated with toluene and dissolved in DCM (2 mL) under argon. After addition of second generation Grubbs catalyst **B** (3 mg, 3.2 μmol, 0.01 equiv), the mixture was refluxed for 1 h. The solvent was evaporated and the product purified by flash column chromatography to yield homogeneous **9** (0.137 g, 0.316 mmol, 99%). IR (thin film) 2932, 2855, 2098, 1470, 1427, 1265, 1184, 1111 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72−7.35 (m, 10H), 6.07−5.92 (m, 2H), 4.27 (m, 1H), 4.10−4.03 (m, 2H), 3.98−3.81 (m, 3H), 2.99 (dd, 1H, J = 7.4, 12.7 Hz), 2.86 (dd, 1H, J = 4.14, 12.7 Hz), 1.09 (s, 9H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 135.7, 133.1, 133.0, 131.1, 130.1, 130.0, 127.8, 122.1, 116.9, 85.6, 82.0, 80.2, 71.9, 64.2, 52.2, 26.9, 19.1; ESI-MS (*m*/*e*) 458.2 $[M + Na]^+$, 893.4 $[2M + Na]^+$; HRMS *m*/*z* calcd for $C_{24}H_{29}N_3O_3SiNa$ 458.1876, obsd 458.1998.

***E*/*Z*-11-[(2*S*,3*R*,4*S*,5*R*)-3-Allyloxy-5-azidomethyl-4-hydroxytetrahydrofuran-2-yl]undec-10-enoic Acid (10).** Anhydroglucitol **8** (2.0 g, 3.2 mmol) was dissolved in THF (15 mL) and cooled to 0 °C. After dropwise addition of tetra-*n*-butylammonium fluoride (1.5 equiv, 4.47 mmol, 3.0 mL 1.6 M in THF) the resulting mixture was allowed to warm to room temperature and stirring was continued for 1 h. Evaporation of the solvent gave the crude product, which was purified by column chromatography (toluene → 2% acetic acid in toluene) to give **10** (1.13 g, 2.86 mmol, 89%) as a mixture of *E*/*Z* isomers. IR (thin film) 3230, 2962, 2932, 2874, 2091, 1717, 1462, 1381, 1381, 1242, 1053 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.95−5.53 (m, 3H), 5.33−5.15 (m, 2H), 4.86 (dd, 0.7H, J = 4.4, 7.7 Hz), 4.48 (dd, 0.3H, J = 4.4, 8.0 Hz), 4.17−4.11 (m, 1H), 4.05−4.01 (m, 1H), 3.93−3.83 (m, 1H), 3.82−3.75 (m, 1H), 3.47−3.43 (m, 2H), 2.38−2.29 (m, 2H), 2.14−2.01 (m, 2H), 1.66−1.56 (m, 2H), 1.41−1.21 (m, 12H); ^{13}C NMR (50.1 MHz, $CDCl_3$), major isomer, δ 179.3, 135.2, 134.1, 124.2, 117.0, 85.8, 83.0, 77.6, 76.4, 71.0, 52.3, 33.9, 29.4, 29.1, 29.0, 28.9, 27.8, 24.6; HRMS *m*/*z* calcd for $C_{20}H_{33}N_3O_5Na$ 418.2312, obsd 418.2322.

Condensation of 10 with Rink Amide Resin. After swelling of Rink amide resin (0.55 mmol/g, 0.80 g, 0.45 mmol) in DMF, a preactivated (1−2 min) mixture of acid **10** (0.36 g, 0.91 mmol, 2 equiv), BOP (0.60 g, 1.35 mmol, 3 equiv), and DiPEA (0.31 mL, 1.8 mmol, 4 equiv) in DMF (2 mL) was added. The mixture was shaken overnight, filtered, washed (DMF 2×, MeOH, DCM, MeOH, DCM, Et_2O), and dried to yield resin **11**.

Isocyanate Reactions. To resin **11** (0.33 g, 0.15 mmol) in DCM (2 mL) were added DiPEA (100 μL, 0.6 mmol, 4 equiv) and either benzyl (92.6 μL, 0.75 mmol, 5 equiv), methoxyphenyl (97.2 μL, 0.75 mmol, 5 equiv), or phenyl (81.7 μL, 0.75 mmol, 5 equiv) isocyanate. The resins were shaken overnight, filtered, washed (DCM, MeOH, DCM, MeOH, DCM, Et_2O), and dried in vacuo to gain resins **12**.

Staudinger Reduction. To resins **12** (0.33 g, 0.15 mmol) in dioxane (2 mL) was added trimethylphosphine (0.75 mmol, 0.75 mL 1 M in toluene). After the mixture was shaken for 1 h, water (0.5 mL) was added and shaking was continued for 0.5 h. The resin was filtered and washed (dioxane, H_2O, dioxane DCM, Et_2O). After repeating the procedure the resins were dried in vacuo.

Coupling of Carbonyl Chlorides. The resins (0.11 g, 0.05 mmol) were swollen in DMF (1 mL) and either diphenylcarbamoyl (58 mg, 0.25 mmol, 5 equiv), benzyloxycarbonyl (36 μL, 0.25 mmol, 5 equiv), or benzoyl (29 μL, 0.25 mmol, 5 equiv) chloride was added. After DiPEA (33 μL, 0.20 mmol, 4 equiv) was added, the mixtures were shaken overnight, filtered, washed (DMF, MeOH, DCM, MeOH, DCM, Et_2O), and dried in vacuo to yield resins **13**.

Ring-Closing Metathesis Cyclization/Cleavage. Resins **13** (0.11 g, 0.05 mmol) were coevaporated with dichloroethane and dispersed in DCM (1 mL) under an argon atmosphere. Grubbs catalyst **B** (2 mg, 2.5 μmol, 5 mol %) was added and the mixtures were refluxed for 16 h. The resins were filtered off and washed with DCM. After concentration of the mother liquor, the residues were taken up in 15% ethyl acetate in toluene and purified by filtration over a silica plug. Washing with the same solution yielded homogeneous pyranofurans **14**.

Pyranofuran 14-1A (24 mg, 48 μmol, 96%): IR (thin film) 3325, 2930, 2871, 1717, 1663, 1508, 1491, 1258, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34−7.14 (m, 15H), 5.99−5.90 (m, 2H), 5.25−5.22 (m, 1H), 5.07−5.03 (m, 1H), 4.87 (d, 1H, J = 3.7 Hz), 4.87 (d, 2H, J = 5.8 Hz), 4.33−4.11 (m, 1H), 4.10−4.08 (m, 1H), 4.33−3.84 (m, 3H), 3.65−3.54 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.3, 155.2, 143.0, 137.6, 131.8, 129.2, 128.7, 128.1, 127.6, 127.5, 125.8, 121.2, 82.1, 80.8, 79.8, 71.5, 64.3, 45.2, 42.9; ESI-MS (*m*/*e*) 500.4 $[M + H]^+$ 522.5 $[M + Na]^+$, 999.4 $[2M + H]^+$; HRMS *m*/*z* calcd for $C_{29}H_{29}N_3O_5H$ 500.2185, obsd 500.2233.

Pyranofuran 14-2A (18 mg, 41 μmol, 82%): IR (thin film) 3325, 2928, 2871, 1717, 1701, 1522, 1508, 1456, 1244, 1142, 1088 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 10H), 6.08−6.01 (m, 2H), 5.40 (m, 1H), 5.10 (s, 2H), 5.04 (m, 1H), 4.91 (d, 1H, J = 3.3 Hz), 4.42−4.31 (m, 2H), 4.24−3.86 (m, 5H), 3.62−3.44 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 155.6, 154.6, 140.1, 131.7, 128.8, 128.4, 128.0, 127.9, 127.7, 121.4, 82.4, 81.0, 79.7, 71.7, 66.6, 64.5, 45.2, 43.2; ESI-MS (*m*/*e*) 439.4 $[M + H]^+$, 461.3 $[M + Na]^+$, 899.5 $[2M + Na]^+$; HRMS *m*/*z* calcd for $C_{24}H_{26}N_2O_6Na$ 461.1688, obsd 461.1723.

Pyranofuran 14-3A (18 mg, 37 μmol, 74%): IR (thin film) 3320, 2924, 2873, 1726, 1653, 1539, 1489, 1456, 1286, 1238, 1167, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76−7.73 (m, 2H), 7.40−7.23 (m, 8H), 6.72−6.70 (m, 1H), 6.08−6.04 (m, 1H), 5.99−5.97 (m, 1H), 5.00 (AB, 2H), 4.96 (d, 1H, J = 3.1 Hz), 4.79 (br s, 1H), 4.53 (m, 2H), 4.16−4.04 (m, 3H), 3.81−3.75 (m, 3H), 3.66−3.61 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.1, 155.6, 137.2, 137.1, 131.8, 129.1, 128.7, 128.4, 128.0, 127.9, 121.3, 118.7, 82.3, 81.1, 79.7, 71.8, 64.5, 54.3, 43.2; ESI-MS (*m*/*e*) 409.1 $[M + H]^+$, 431.2 $[M + Na]^+$; HRMS *m*/*z* calcd for $C_{23}H_{24}N_2O_5Na$ 431.1582, obsd 431.1625.

Pyranofuran 14-1B (26 mg, 50 μmol, 99%): IR (thin film) 3265, 2930, 2835, 1724, 1653, 1599, 1510, 1489, 1416, 1298, 1265, 1217, 1178, 1090, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33−7.24 (m, 11H), 7.20−7.16 (m, 2H), 6.90 (br s, 1H), 6.84−6.80 (m, 2H), 6.01−5.91 (m, 2H), 5.22 (br t, 1H, J = 5.2 Hz), 4.91 (d, 1H, J = 3.8 Hz), 4.14 (dd, 1H, J = 4.8, 8.8 Hz), 4.08−4.07 (br s, 1H), 4.02−3.89 (m, 3H), 3.78 (s, 3H), 3.78 (app t, 2H, J = 5.1 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.4, 152.6, 142.9, 131.8, 130.6, 128.8, 127.5, 125.9, 121.2, 114.2, 81.9, 80.8, 79.8, 71.6, 64.4, 55.5, 42.8; ESI-MS (*m*/*e*) 516.2 $[M + H]^+$, 538.2 $[M + Na]^+$; HRMS *m*/*z* calcd for $C_{29}H_{29}N_3O_6Na$ 538.1954, obsd 538.1964.

Pyranofuran 14-2B (20 mg, 45 μmol, 89%): IR (thin film) 3312, 2927, 2848, 1717, 1705, 1541, 1514, 1456, 1221, 1180, 1092, 1032 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.26 (m, 7H), 6.87−6.84 (m, 2H), 6.54 (br s, 1H), 6.10−5.99 (m, 2H), 5.37−5.35 (m, 1H), 5.07 (s, 2H), 4.26−4.02 (m, 5H), 3.79 (s, 3H), 3.64−3.47 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.7, 153.6, 140.1, 132.2, 131.7, 128.9, 128.4, 128.3, 121.8, 114.7,

82.7, 81.5, 80.1, 72.1, 67.0, 64.9, 55.9, 43.6; ESI-MS (*m*/*e*) 455.3 $[M + H]^+$, 477.0 $[M + Na]^+$, 931.2 $[2M + Na]^+$; HRMS *m*/*z* calcd for $C_{24}H_{26}N_2O_7Na$ 477.1637, obsd 477.1670.

Pyranofuran 14-3B (17 mg, 40 μmol, 80%): IR (thin film) 3270, 2924, 2869, 1724, 1647, 1602, 1541, 1514, 1489, 1298, 1225, 1180, 1092, 1034 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.80 (m, 2H), 7.48−7.26 (m, 5H), 7.06−7.04 (m, 1H), 6.87−6.84 (m, 2H), 6.65 (br s, 1H), 6.13−6.05 (m, 2H), 5.07 (d, 2H J = 3.0 Hz), 4.28−4.15 (m, 4H), 4.07 (d, 1H, J = 2.3 Hz), 3.90−3.71 (m, 2H), 3.79 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.1, 153.0, 134.5, 131.8, 131.3, 130.1, 128.4, 127.0, 121.3, 120.7, 114.3, 82.3, 81.1, 79.7, 71.7, 64.7, 55.5, 42.1; ESI-MS (*m*/*e*) 424.9 $[M + H]^+$, 447.2 $[M + Na]^+$, 871.4 $[2M + Na]^+$; HRMS *m*/*z* calcd for $C_{23}H_{24}N_2O_6H$ 425.1712, obsd 425.1750.

Pyranofuran 14-1C (20 mg, 49 μmol, 98%): IR (thin film) 3260, 2924, 2853, 1730, 1651, 1599, 1541, 1514, 1489, 1445, 1369, 1315, 1300, 1271, 1219, 1184, 1090, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36−7.24 (m, 12H), 7.20−7.16 (m, 2H), 7.08−7.04 (m, 1H), 6.95 (br s, 1H), 6.02−5.92 (m, 2H), 5.22 (br t, 1H, J = 5.1 Hz), 4.93 (d, 1H, J = 3.7 Hz), 4.14 (dd, 1H, J = 4.8, 8.8 Hz), 4.09−4.07 (m, 1H), 4.03−3.95 (m, 3H), 3.78 (s, 3H), 3.64−3.61 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.3, 152.2, 142.9, 137.5, 131.8, 129.2, 129.0, 127.5, 126.0, 123.6, 121.2, 118.7, 81.9, 81.0, 79.8, 71.6, 64.4, 42.9; ESI-MS (*m*/*e*) 486.2 $[M + H]^+$, 508.2 $[M + Na]^+$, 993.4 $[2M + Na]^+$; HRMS *m*/*z* calcd for $C_{28}H_{27}N_3O_5H$ 486.2028, obsd 486.2059.

Pyranofuran 14-2C (18 mg, 42 μmol, 85%): IR (thin film) 3309, 2924, 2853, 1703 1601, 1541, 1501, 1445, 1315, 1219, 1184, 1151, 1090, 1028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.26 (m, 9H), 7.12−7.07 (m, 1H), 6.71 (br s, 1H), 6.10−5.99 (m, 2H), 5.37−5.35 (m, 1H), 5.10 (s, 2H), 4.97 (d, 1H, J = 3.5 Hz), 4.27−4.03 (m, 5H), 3.64−3.49 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 154.8, 152.7, 137.2, 137.1, 131.8, 129.1, 128.7, 128.4, 128.0, 127.9, 121.3, 118.7, 82.3, 81.1, 79.7, 71.8, 66.6, 64.5, 43.2; ESI-MS (*m*/*e*) 425.1 $[M + H]^+$, 447.1 $[M + Na]^+$, 871.5 $[2M + Na]^+$; HRMS *m*/*z* calcd for $C_{23}H_{24}N_2O_6H$ 425.1712, obsd 425.1750.

Pyranofuran 14-3C (15 mg, 38 μmol, 76%): IR (thin film) 3280, 2924, 2869, 1734, 1717, 1647, 1603, 1541, 1447, 1315, 1221, 1092, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.83−7.80 (m, 2H), 7.48−7.26 (m, 7H), 7.13−7.08 (m, 1H), 7.03−7.01 (m, 1H), 6.71 (br s, 1H), 6.14−6.07 (m, 2H), 5.09 (d, 2H J = 3.1 Hz), 4.32−4.15 (m, 4H), 4.08 (d, 1H, J = 2.6 Hz), 3.92−3.72 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 156.1, 152.7, 137.2, 137.1, 131.8, 129.1, 128.7, 128.4, 128.0, 127.9, 121.3, 118.7, 82.3, 81.1, 79.7, 71.7, 64.8, 42.1; ESI-MS (*m*/*e*) 395.1 $[M + H]^+$, 417.2 $[M + Na]^+$, 811.3 $[2M + Na]^+$; HRMS *m*/*z* calcd for $C_{22}H_{22}N_2O_5Na$ 417.1426, obsd 417.1444.

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Supporting Information Available: Spectral data (^1H NMR) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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