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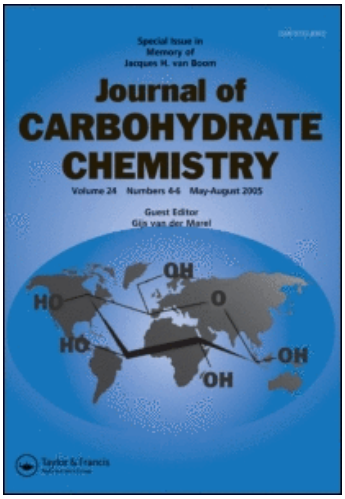

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Selective Cross-Metathesis of *C*-Allyl-Glycosides

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Selective Cross-Metathesis of *C*-Allyl-Glycosides

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The efficient and selective cross-metathesis (CM) of both the α- and β-anomers of *C*-allyl-glucose and *N*-acetyl-*C*-allyl-glucosamine with electron-deficient olefins is reported. The applicability of our CM approach in the synthesis of glycoside-conjugates is illustrated by the CM of α-*C*-allyl-glycosamine **2** with uridinyl vinylphosphonate **22**, to produce UDP-GlcNAc analog **23**.

Keywords Synthesis, Cross-metathesis, C-glycosides, UDP-GlcNAc, Inhibitor

INTRODUCTION

Olefin metathesis has become an increasingly important and powerful tool in organic chemistry.[1] The success of olefin metathesis is largely due to the development of stable, reactive, and functional group-tolerant precatalysts, the most important examples of which are the ruthenium alkylidenes **I** and **II** (Fig. 1).[2] The great potential of olefin metathesis is illustrated by the recent advances in the synthesis of disubstituted olefins by cross-metathesis (CM) reactions.[3] Although several types of alkenes have been applied in CM

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†With deep sadness the authors inform the reader that our colleague, Jacques H. van Boom, died on July 31, 2004 at the age of 67.
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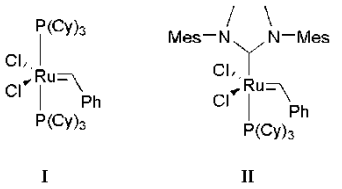
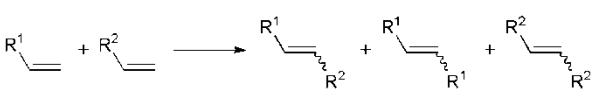


I II

Figure 1: Olefin metathesis precatalysts.

using the first-generation ruthenium precatalysts **I**,[4] nonterminal and conjugated olefins in general are poor substrates in combination with this catalyst. Since the emergence of the *N*-heterocyclic carbene (NHC) coordinated precatalysts,[5] such as the second-generation Grubbs' precatalyst **II**, both nonterminal and conjugated olefins can now participate in productive CM events.[6] Theoretically, CM of two differently substituted terminal alkenes (**A** and **B**) can lead to the formation of up to six products (Sch. 1).

Besides the desired heterodimeric product(s) **C**, two undesired homodimeric products (**D** and **E**) can be formed, all as a mixture of *E* and *Z* isomers. Major goals in the area of CM comprise the acquirement of product selectivity and control over *E*/*Z* ratios. One of the first examples of a ruthenium complex **I**-catalyzed CM is the heterodimerization of the electron-rich allyltrimethylsilane[7] and a variety of aliphatic alkenes. Although high product selectivity was obtained, the *E*/*Z*-selectivity was low. Blechert and coworkers have shown that product selectivity can be increased by using Grubbs' second-generation precatalyst **II** in the CM of sterically hindered terminal olefins, which proved to undergo selective CM with a variety of commercially available terminal olefins.[8] On the other hand, Grubbs and coworkers have developed a two-step CM procedure in which terminal olefins are first homodimerized prior to a second CM event with a second alkene, leading to heterodimers with considerably improved reaction rates and high *E*-selectivity.[9] Recently, it has become evident that a combination of aliphatic olefins with more electrophilic alkenes, such as α,β-unsaturated esters, ketones, and phosphonates, leads to good product selectivities.[10] The unreactive electron-poor alkene is prohibited to undergo self-metathesis, while the aliphatic olefin can, after homodimerization, undergo a second metathesis event with the α,β-unsaturated alkene to form the desired product. In this paper we report the ruthenium complex **II**-catalyzed CM of *C*-allyl-glycosides, bearing an electron-rich double bond,



A B C D E

Scheme 1: Olefin cross-metathesis products.

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with electron-poor alkenes to give anomerically functionalized *C*-glycosides. Some initial results in the assessment of inhibitory activity against *N*-acetyl-glucosamine processing enzymes are presented.

RESULTS AND DISCUSSION

The *C*-allyl-glucosides (**1–4**), which we have selected for CM with a set of commercially available α,β-unsaturated alkenes (**5–7**), are depicted in Figure 2. Both the α- and β-anomers of *C*-allyl-D-glucose and *N*-acetyl-*C*-allyl-D-glucosamine were readily accessible through known procedures.[11–14]

The α-*C*-allyl-glucopyranoside **1** was treated with 5 mol% of Grubbs' precatalyst **II** and five equivalents of dimethyl vinylphosphonate (**5**) in DCM, under an argon atmosphere. After refluxing for 14 hr, TLC-analyses showed complete disappearance of **1** and the formation of a more polar compound. Work-up and purification by silica gel column chromatography led to the isolation of pure *E*-glucosylphosphonate **8** in 71% yield (entry 1, Table 1). We were quite pleased to see that only a trace amount, as judged by the relative intensities of the corresponding ^{1}H NMR signals, of the *Z*-product was formed. Subjection of *N*-acetyl-*C*-allyl-D-glucosamine **2** to the above-mentioned CM conditions proceeded uneventfully to give *E*-glucosaminophosphonate **9** in a satisfying yield of 72% (entry 2). The series of glyco-phosphonates was completed by a similar treatment of the β-*C*-glucosides **3** and **4**, which afforded phosphonates **10** and **11** yields of 85% and 84%, respectively (entries 3 and 4), again with only trace amounts of the *Z*-isomers. Next, the set of glucosides (**1–4**) was subjected to CM with *tert*-butyl acrylate (**6**). Again, selective CM was achieved resulting in *tert*-butyl glucosylacrylates **12–15** (entries 5–8) in excellent yields, ranging from 74% to 93%. Similar results were obtained in the CM of glucosides **1–4** with acrylic acid (**7**) and 3-glucosyl-acrylic acids **16–19** could be isolated in

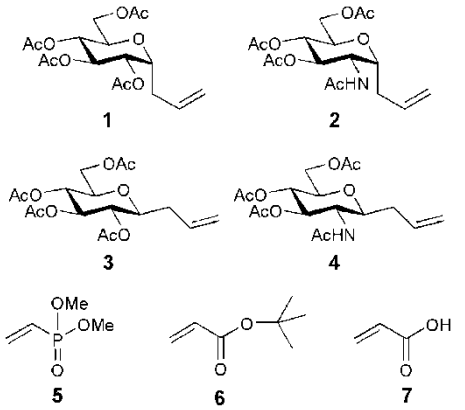

Figure 2: *C*-allyl-glycosides and electron-deficient alkenes.

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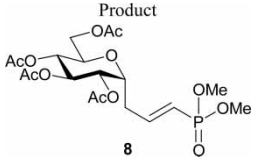
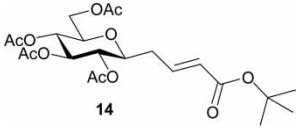
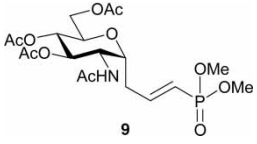
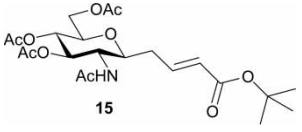
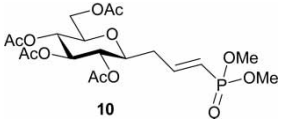
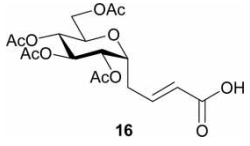
Table 1: CM of *C*-allyl-glycosides with electron-deficient alkenes.[a]

Entry	Alkenes		Product	Yield[b]	Entry	Alkenes		Product	Yield[b]
1	**1**	**5**	 **8**	71	7	**3**	**6**	 **14**	87
2	**2**	**5**	 **9**	72	8	**4**	**6**	 **15**	74
3	**3**	**5**	 **10**	85	9	**1**	**7**	 **16**	82

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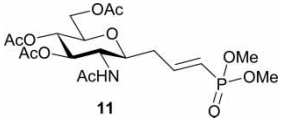
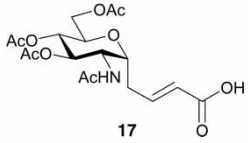
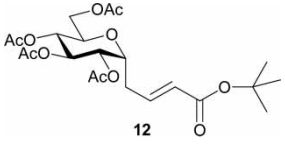
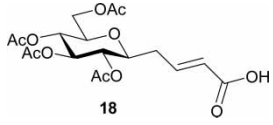
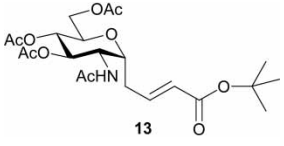
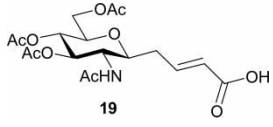
4	**4**	**5**		84	10	**2**	**7**		81
5	**1**	**6**		90	11	**3**	**7**		78
6	**2**	**6**		93	12	**4**	**7**		72

[a]Reagents and conditions: **II** (5 mol%), DCM, reflux, Ar, 14 hr.
[b]Yield of isolated products.

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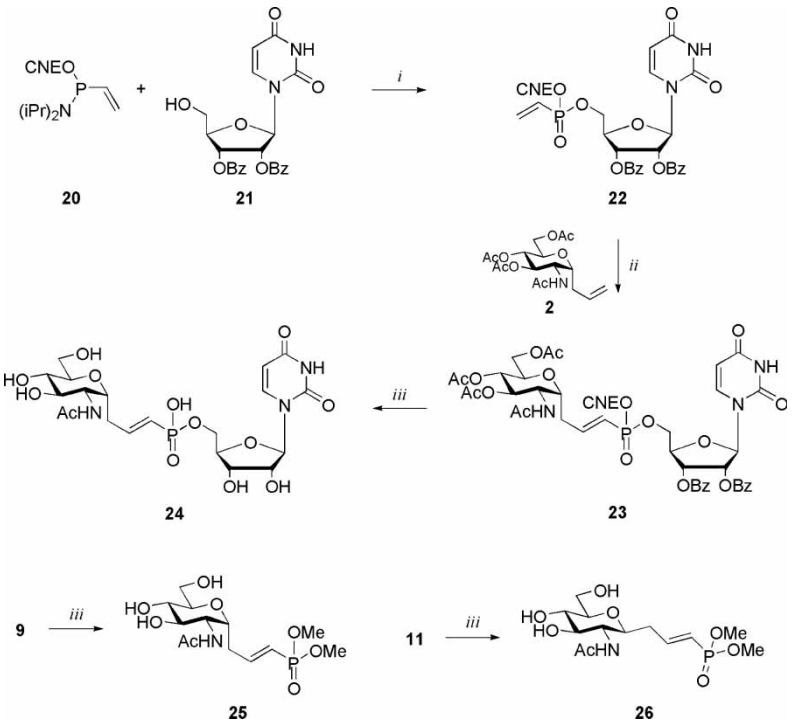
72% to 82% (entries 9–12). The outcome of this study clearly demonstrates that CM is an efficient approach to carbohydrate derivatives that are functionalized differently at the anomeric center. Application of more intricate electrophilic alkenes should allow the synthesis of advanced *C*-glycoside-conjugates. In this framework, we set out to apply our CM approach to the synthesis of UDP-GlcNAc analog **23** (Sch. 2).

The required uridinyl vinylphosphonate **22** was readily obtained via a phosphorylation strategy developed earlier in our laboratory.[15] Condensation of 2′,3′-benzoyl-uridine **20** with the cyanoethyl (CNE)-protected phosphoramidite **21** using 1*H*-tetrazole as the activating agent followed by in situ oxidation of the intermediate phosphine with *tert*-butyl hydrogenperoxide led to the isolation of uridinyl vinylphosphonate **22** in 73% over the two steps. Unfortunately, treatment of uridinyl phosphonate **22** and α-*C*-allyl-glucosamide **2** with precatalyst **II** under the earlier mentioned conditions only led to trace amounts of the expected product **23**. These results are in accordance with the study of Lera et al. on the CM of CNE-protected vinylphosphonates.[6d] It occurred to us that the use of copper(I) chloride, applied by Blechert and coworkers in their CM studies of acrylonitrile,[16] could have a beneficial



Scheme 2: Synthesis of UDP-GlcNAc analog **24**. Reagents and conditions: (*i*) 1*H*-tetrazole (3) equiv.), MeCN, RT, Ar, then *t*BuOOH, 0°C, 5 min, 73%. (*ii*) **II** (5 mol%), CuCl (20 mol%), DCM, reflux, Ar, 3 hr, 58%, *E*/*Z* = 8:1. (*iii*) NaOMe, MeOH, RT, 16 hr, 75% (**24**), 95% (**25**), 95% (**26**).

effect on the yield of **23**. Gratifyingly, execution of the CM of **2** and **22** with 5 mol% Grubbs′ precatalyst II in combination with 20 mol% copper(I) chloride gave the protected UDP-GlcNAc conjugate **23** as an 8:1 mixture of *E*- and *Z*-isomers, in 58% yield. HPLC purification led to the homogeneous *E*-isomer, the identity of which was fully ascertained by NMR and HRMS. To determine the inhibitory potential of the α,β-unsaturated phosphonates, compound **23** as well as the α- and β-glucosamine phosphonates **9** and **11** were deprotected under basic conditions to give neoglycosides **24**, **25**, and **26**.

The inhibitory potency of **24**, **25**, and **26** was tested toward human β-hexosamidase purified from spleen and recombinant human chitinase (chitotriosidase), an endo-β-D-*N*-acetylglucosaminidase.[17] The outcome of these studies showed that compounds **25** and **26** are only weak inhibitors at 1 mM concentrations, whereas for compound **24** no inhibition was observed. Studies on the inhibitory activities of **24**–**26** in a standard *N*-acetyl-D-glucosaminyltransferase[18] assay revealed that none of these compounds was able to inhibit *N*-acetyl-D-glucosaminyltransferase activity.

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CONCLUSION

In conclusion, we have presented a short and efficient synthesis of anomerically functionalized α- and β-*C*-glycosides, from inexpensive, readily available precursors by way of a ruthenium-based olefin CM reaction. The viability of this procedure is exemplified in the synthesis of UDP-GlcNAc analog **24** and both α- and β-glucosamine-phosphonates **25** and **26**. Biologic screening indicates that these compounds are poor inhibitors of human lysosomal β-hexosaminidase isolated from spleen, recombinant human chitinase, and an *N*-acetyl-D-glucosaminyltransferase.

EXPERIMENTAL

General Methods and Materials

All reactions were performed dry, under an inert atmosphere and at ambient temperature unless stated otherwise. Toluene (purum), ethyl acetate (puriss.), and light petroleum ether (puriss.) were obtained from Riedel-de Haën and distilled prior to use. Acetonitrile, dichloromethane, and diethyl ether (Biosolve) were stored on 4Å molecular sieves. THF (Biosolve) was distilled from $LiAlH_4$ prior to use. Acrylic acid (Merck) was distilled prior to use. *tert*-Butyl acrylate (Aldrich), *tert*-butyl hydroperoxide (Fluka), dimethyl vinylphosphonate (Fluka), methanol (Biosolve), 1*H*-tetrazole (Acros), and triethylamine (Acros) were used as received. All solvents were removed by evaporation under reduced pressure. Reactions were monitored

by TLC analysis using DC-fertigfolien (Schleicher & Schuell, F1500, LS254) with detection by UV-absorption (254 nm), by spraying with an aqueous solution of $KMnO_4$ (7%) and KOH (2%), by spraying with 20% H_2SO_4 in ethanol followed by charring at ~150°C, or by spraying with a solution of $(NH_4)_6Mo_7O_{24} \cdot 4H_2O$ (25 g/L) and $(NH_4)_4Ce(SO_4)_4 \cdot 2H_2O$ (10 g/L) in 10% sulfuric acid followed by charring at ~150°C. Column chromatography was performed on Merck silicagel (0.040–0.063 nm). Mass spectra were recorded on a PE/Sciex API 165 instrument and HRMS (SIM mode) were recorded on a TSQ Quantum (Thermo Finnigan) fitted with an accurate mass option, interpolating between PEG-calibration peaks. ^1H, ^{13}C-APT, and ^{31}P NMR spectra were recorded on a Jeol JNM-FX-200 (200/50.1/81.1 MHz), a Brüker WM-300 (300/75.1/121 MHz), a Brüker AV-400 (400/100/162 MHz), or a Brüker DMX-600 (600/150/242 MHz) spectrometer. Chemical shifts are given in ppm (δ) relative to tetramethylsilane (^1H NMR and ^{13}C NMR) or 85% H_3PO_4 (^{31}P NMR). Coupling constants (J) are given in Hz. Where indicated, NMR peak assignments were made using COSY and NOESY experiments. All presented ^{13}C-APT and ^{31}P spectra are proton decoupled. Optical rotations were measured on a Propol automatic polarimeter (Sodium D line, $\lambda = 589$ nm) and ATR-IR spectra were recorded on a Shimadzu FTIR-8300 fitted with a single bounce DurasamplIR diamond crystal ATR-element.

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General procedure for the cross-metathesis of glycosides 1–4 with electron-deficient alkenes 5–7. The electron-deficient alkene (5 equiv.) and Grubbs' second-generation precatalyst **II** (0.05 equiv.) were added to a solution of the *C*-allyl-glycoside in DCM (5 mL/mmol) under an argon atmosphere. After refluxing for 14 hr, the mixture was concentrated and purified by silica gel column chromatography (ethyl acetate → 5% methanol in ethyl acetate).

Dimethyl *E*-3-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-propenylphosphonate (8). Cross-metathesis of **1** (140 mg, 0.376 mmol) and dimethyl vinylphosphonate (2 mmol) using the general procedure described above yielded **8** as a colorless oil (128 mg, 0.267 mmol, 71%, $E/Z = 16{:}1$): $[\alpha]_D^{20} = +68.2°$ ($c = 1.0$, $CHCl_3$); IR (thin film) 2955, 1738, 1636, 1435, 1373, 1213, 1142, 1097, 1024, 980, 939, 907, 826 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.74 (ddt, $J_{2,P} = 21.9$, $J_{1,2} = 17.2$, $J_{2,3a} = J_{2,3b} = 6.6$, 1H, H-2), 5.81 (ddt, $J_{1,P} = 20.0$, $^4J_{1,3a} = {}^4J_{1,3b} = 1.6$, 1H, H-1), 5.30 (dd, $J_{2',3'} = 9.2$, $J_{3',4'} = 8.5$, 1H, H-3′), 5.10 (dd, $J_{1',2'} = 5.6$, 1H, H-2′), 4.97 (dd, $J_{4',5'} = 9.1$, 1H, H-4′), 4.36 (ddd, $J_{1',3a} = 5.6$, $J_{1',3b} = 4.3$, 1H, H-1′), 4.26 (dd, $J_{5',6a'} = 5.7$, $^2J_{6a',6b'} = 12.3$, 1H, H-6a′), 4.05 (dd, $J_{5',6b'} = 2.7$, 1H, H-6b′), 3.86 (ddd, 1H, H-5′), 3.724 (d, $J = 11.0$, 3H, CH_3OP), 3.722 (d, $J = 11.0$, 3H, CH_3OP), 2.73 (ddddd, $J_{3a,P} = 22.8$, $J_{3a,3b} = 2.4$, 1H, H-3a), 2.73 (ddddd, $J_{3b,P} = 16.0$, 1H, H-3b), 2.11 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.048 (s, 3H, CH_3), 2.045 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.7, 170.0, 169.5, 169.4 (C=O), 148.1 (d, $J_P = 5.4$, C-2), 119.1 (d, $J_P = 189$, C-1), 71.0 (C-1′), 69.9 (C-3′), 69.8 (C-2′),

69.3 (C-5′), 68.5 (C-4′), 61.9 (C-6′), 52.3 (d, $J_P = 5.7$, CH_3OP), 30.9 (d, $J_P = 23.3$, C-4), 20.60 (CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.4; ESI-MS (m/z): 481.1 $[M + H]^+$, 503.1 $[M + Na]^+$, 983.4 $[2M + Na]^+$; HRMS m/z calcd. for $C_{19}H_{29}O_{12}P$: 481.1469, obsd: 481.1479.

Dimethyl *E*-3-(2-acetamido-3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranosyl)-propenylphosphonate (9). Cross-metathesis of **2** (123 mg, 0.332 mmol) and dimethyl vinylphosphonate (2 mmol) using the general procedure described above yielded **9** as a colorless oil (115 mg, 0.240 mmol, 72%, $E/Z = 19{:}1$): $[\alpha]_D^{20} = +42.0^\circ$ ($c = 1.0$, $CHCl_3$); IR (thin film) 2955, 1744, 1670, 1635, 1541, 1437, 1369, 1229, 1030, 988, 908, 826, 725, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.67 (ddt, $J_{2,P} = 22.0$, $J_{1,2} = 17.2$, $J_{2,3a} = J_{2,3b} = 6.6$, 1H, H-2), 6.47 (d, $J_{NH,2'} = 8.3$, 1H, NH), 5.72 (dd, $J_{1,P} = 20.6$, 1H, H-1), 4.99 (t, $J_{2',3'} = J_{3',4'} = 6.7$, 1H, H-3′), 4.84 (t, $J_{4',5'} = 6.7$, 1H, H-4′), 4.31 (dd, $J_{5',6a'} = 6.6$, $^2J_{6a',6b'} = 12.2$, 1H, H-6a′), 4.23 (m, 2H, H-1′ and H-2′), 4.01 (dd, $J_{5',6b'} = 3.4$, 1H, H-6b′), 3.87 (dt, 1H, H-5′), 3.66 (d, $J_P = 11.0$, 3H, CH_3OP), 3.65 (d, $J_P = 11.0$, 3H, CH_3OP), 2.54 (m, 1H, H-3a), 2.41 (m, 1H, H-3b), 2.05 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.93 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.5, 170.2, 169.8, 168.8 (C═O), 148.7 (d, $J_P = 4.9$, C-2), 118.3 (d, $J_P = 188$, C-1), 70.8 (C-1′), 69.7 (C-5′), 69.3 (C-3′), 67.6 (C-4′), 61.0 (C-6′), 52.1 (d, $J_P = 4.5$, CH_3OP), 49.7 (C-2′), 32.4 (d, $J_P = 22.7$, C-3), 22.8, 20.6, 20.5, 20.4 (CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.4; ESI-MS (m/z): 480.0 $[M + H]^+$, 502.2 $[M + Na]^+$, 981.3 $[2M + Na]^+$; HRMS m/z calcd. for $C_{19}H_{30}NO_{11}P$: 480.1629, obsd: 480.1645.

***E*-Dimethyl 3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-propenylphosphonate (10).** Cross-metathesis of **3** (137 mg, 0.368 mmol) and dimethyl vinylphosphonate (2 mmol) using the general procedure described above yielded **10** as a colorless oil (150 mg, 0.313 mmol, 85%, $E/Z = 24{:}1$): $[\alpha]_D^{20} = -4.8^\circ$ ($c = 1.0$, $CHCl_3$); IR (thin film) 2943, 1744, 1636, 1437, 1215, 1140, 1099, 1026, 990, 908, 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (ddt, $J_{2,P} = 22.0$, $J_{1,2} = 17.2$, $J_{2,3a} = J_{2,3b} = 6.7$, 1H, H-2), 5.72 (ddt, $J_{1,P} = 20.4$, $^4J_{1,3a} = {}^4J_{1,3b} = 1.5$, 1H, H-1), 5.18 (t, $J_{2',3'} = J_{3',4'} = 9.5$, 1H, H-3′), 5.04 (t, $J_{4',5'} = 9.5$, 1H, H-4′), 4.90 (t, $J_{1',2'} = 9.5$, 1H, H-2′), 4.23 (dd, $J_{5',6a'} = 5.2$, $^2J_{6a',6b'} = 12.3$, 1H, H-6a′), 4.08 (dd, $J_{5',6b'} = 2.3$, 1H, H-6b′), 3.72 (d, $J = 11.0$, 6H, CH_3OP), 3.66 (ddd, 1H, H-5′), 3.59 (ddd, $J_{1',3a} = 4.2$, $J_{1',3b} = 7.5$, 1H, H-1′), 2.47 (m, 2H, H-3a and H-3b), 2.09 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.00 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.5, 170.2, 169.5, 169.4 (C = O), 148.3 (d, $J_P = 5.3$, C-2), 118.8 (d, $J_P = 188$, C-1), 76.0 (C-1′), 75.6 (C-5′), 74.1 (C-3′), 71.5 (C-2′), 68.3 (C-4′), 62.0 (C-6′), 52.2 (d, $J_P = 5.2$, CH_3OP), 36.0 (d, $J_P = 22.9$, C-4), 20.53, 20.47 (CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.7; ESI-MS (m/z): 481.2 $[M + H]^+$, 503.1 $[M + Na]^+$, 983.4 $[2M + Na]^+$; HRMS m/z calcd. for $C_{19}H_{29}O_{12}P$: 481.1469, obsd: 481.1479.

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Dimethyl *E*-3-(2-acetamido-3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-propenylphosphonate (11). Cross-metathesis of **4** (93 mg, 0.25 mmol) and dimethyl vinylphosphonate (1.25 mmol) using the general procedure described above yielded **11** as a colorless oil (99 mg, 0.21 mmol, 84%, $E/Z = 12{:}1$): $[\alpha]_D^{20} = -20.0^\circ$ ($c = 0.1$, $CHCl_3$); IR (thin film) 2916, 1734, 1651, 1560, 1452, 1373, 1236, 1078, 1034, 980, 907, 835 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (ddt, $J_{2,P} = 22.1$, $J_{2,3} = 17.2$, $J_{2,3a} = J_{2,3b} = 6.6$, 1H, H-2), 5.89 (d, $J_{NH,2'} = 9.3$, 1H, NH), 5.72 (ddt, $J_{1,P} = 20.9$, $^4J_{1,3a} = {}^4J_{1,3b} = 1.5$, 1H, H-1), 5.04 (m, 2H, H-3′ and H-4′), 4.21 (dd, $J_{5',6a'} = 5.2$, $^2J_{6a',6b'} = 12.3$, 1H, H-6a′), 4.08 (dd, $J_{5',6b'} = 2.3$, 1H, H-6b′), 4.03 (ddd, $J_{2',3'} = 9.6$, $J_{1',2'} = 10.1$, 1H, H-2′), 3.72 (d, 6H, $(CH_3O)_2P$), 3.60 (ddd, $J_{4',5'} = 9.6$, 1H, H-5′), 3.45 (ddd, $J_{1',3a} = 3.9$, $J_{1',3b} = 8.0$, 1H, H-1′), 2.53 (m, 2H, H-3a and H-3b), 2.09 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.95 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.5, 170.7, 170.3, 169.3 (C═O), 149.7 (d, $J_P = 5.1$, C-3), 123.3 (d, $J_P = 188$, C-2), 77.8 (C-1′), 75.7 (C-5′), 74.1 (C-3′), 68.4 (C-4′), 62.3 (C-6′), 53.7 (C-2′), 52.3 (CH_3O), 36.5 (d, $J = 22.8$, C-4), 23.1, 20.7, 20.6 (CH_3); ESI-MS (m/z): 480.1 $[M + H]^+$, 502.2 $[M + Na]^+$, 959.6 $[2M + H]^+$, 981.6 $[2M + Na]^+$; HRMS m/z calcd. for $C_{19}H_{30}NO_{11}P$: 480.1629, obsd: 480.1688.

***E*-4-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-but-2-enoic acid *tert*-butyl ester (12).** Cross-metathesis of **1** (138 mg, 0.371 mmol) and *tert*-butyl acrylate (2 mmol) using the general procedure described above yielded **12** as a white solid (158 mg, 0.335 mmol, 90%, $E/Z = 14{:}1$): $[\alpha]_D^{20} = +68.2^\circ$ ($c = 1.0$, $CHCl_3$); IR (thin film) 2950, 1742, 1711, 1653, 1437, 1367, 1213, 1151, 1092, 1030, 980, 912, 847 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (dt, $J_{2,3} = 15.6$, $J_{3,4a} = J_{3,4b} = 6.8$, 1H, H-3), 5.88 (ddd, $^4J_{2,4a} = 1.2$, $^4J_{2,4b} = 1.5$, 1H, H-2), 5.32 (t, $J_{2',3'} = J_{3',4'} = 9.2$, 1H, H-3′), 5.11 (dd, $J_{1',2'} = 5.6$, 1H, H-2′), 4.96 (t, 1H, H-4′), 4.35 (ddd, $J_{1',4a} = 10.2$, $J_{1',4b} = 4.8$, 1H, H-1′), 4.24 (dd, $J_{5',6a'} = 5.9$, $^2J_{6a',6b'} = 12.2$, 1H, H-6a′), 4.07 (dd, $J_{5',6b'} = 2.5$, 1H, H-6b′), 3.86 (ddd, 1H, H-5′), 2.68 (dddd, 1H, H-4a), 2.45 (dddd, 1H, H-4b), 2.09 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 1.47 (s, 9H, *t*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.6, 170.0, 169.4, 165.1 (C═O, C-1), 141.5 (C-3), 125.8 (C-2), 80.4 (C_q *t*-Bu), 71.3 (C-1′), 69.9 (C-5′), 69.8 (C-3′), 69.0 (C-2′), 68.8 (C-4′), 62.0 (C-6′), 28.7 (C-4), 28.0 (CH_3 *t*-Bu), 20.6 (CH_3); ESI-MS (m/z): 473.2 $[M + H]^+$, 495.4 $[M + Na]^+$, 945.5 $[2M + H]^+$, 967.6 $[2M + Na]^+$; HRMS m/z calcd. for $C_{22}H_{32}O_{11}$: 473.2017, obsd: 473. 2068.

***E*-4-(2-acetamido-3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranosyl)-but-2-enoic acid *tert*-butyl ester (13).** Cross-metathesis of **2** (140 mg, 0.377 mmol) and *tert*-butyl acrylate (2 mmol) using the general procedure described above yielded **13** as a white solid (165 mg, 0.350 mmol, 93%, $E/Z = 10{:}1$): $[\alpha]_D^{20} = +42.8^\circ$ ($c = 1.0$, $CHCl_3$); IR (thin film) 2980, 2936, 1740, 1712, 1684, 1653, 1541, 1437, 1367, 1221, 1153, 1090, 1034, 980,

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912, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.81 (dt, $J_{2,3} = 15.7$, $J_{3,4a} = J_{3,4b} = 7.2$, 1H, H-3), 6.34 (d, $J_{NH,2'} = 8.6$, 1H, NH), 5.86 (d, 1H, H-2), 5.07 (t, $J_{2',3'} = J_{3',4'} = 6.9$, 1H, H-3′), 4.91 (t, $J_{4',5'} = 6.9$, 1H, H-4′), 4.37 (dd, $J_{5',6a'} = 7.4$, $^2J_{6a',6b'} = 12.1$, 1H, H-6a′), 4.30 (m, 2H, H-1′ and H-2′), 4.10 (dd, $J_{5',6b'} = 3.3$, 1H, H-6b′), 3.95 (ddd, 1H, H-5′), 2.48 (m, 2H, H-4a and H-4b), 2.09 (s, 3H, CH_3), 2.087 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 1.99 (s, 3H, CH_3), 1.47 (s, 9H, *t*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.4, 170.3, 169.7, 168.8, 165.0 (C═O, C-1), 142.0 (C-3), 125.4 (C-2), 80.1 (C_q *t*-Bu), 70.7, 70.0, 69.7, 67.7 (C-1′, C-3′, C-4′, C-5′), 61.8 (C-6′), 51.0 (C-2′), 30.2 (C-4), 27.9 (CH_3 *t*-Bu), 22.8, 20.54, 20.47, 20.39 (CH_3); ESI-MS (m/z): 472.2 $[M + H]^+$, 494.2 $[M + Na]^+$, 943.7 $[2M + H]^+$, 965.5 $[2M + Na]^+$; HRMS m/z calcd. for $C_{22}H_{33}NO_{10}$: 472.2177, obsd: 472.2212.

***E*-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-but-2-enoic acid *tert*-butyl ester (14).** Cross-metathesis of **3** (135 mg, 0.363 mmol) and *tert*-butyl acrylate (2 mmol) using the general procedure described above yielded **14** as a white solid (148 mg, 0.314 mmol, 87%, $E/Z = 21{:}1$): $[\alpha]_D^{20} = -4.4^\circ$ ($c = 1.0$, $CHCl_3$); IR (thin film) 2937, 1747, 1712, 1653, 1435, 1367, 1213, 1153, 1101, 1030, 980, 907, 849 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.79 (dt, $J_{2,3} = 15.7$, $J_{3,4a} = J_{3,4b} = 6.9$, 1H, H-3), 5.78 (d, 1H, H-2), 5.16 (t, $J_{2',3'} = J_{3',4'} = 9.5$, 1H, H-3′), 5.03 (t, $J_{4',5'} = 9.5$, 1H, H-4′), 4.89 (t, 1H, H-2′), 4.22 (dd, $J_{5',6a'} = 5.2$, $^2J_{6a',6b'} = 12.3$, 1H, H-6a′), 4.07 (dd, $J_{5',6b'} = 2.2$, 1H, H-6b′), 3.65 (ddd, 1H, H-5′), 3.55 (dt, $J_{1',4a} = 6.0$, $J_{1',4b} = 9.5$, 1H, H-1′), 2.39 (m, 2H, H-4a and H-4b), 2.08 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 1.46 (s, 9H, *t*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.5, 170.2, 169.4, 169.3, 165.3 (C═O, C-1), 141.5 (C-3), 125.5 (C-2), 80.2 (C_q *t*-Bu), 76.3 (C-1′), 75.6 (C-5′), 74.1 (C-3′), 71.7 (C-2′), 68.5 (C-4′), 62.1 (C-6′), 34.1 (C-4), 28.0 (CH_3 *t*-Bu), 20.6, 20.5 (CH_3); ^{31}P NMR (162 MHz, $CDCl_3$): δ 21.7; ESI-MS (m/z): 473.4 $[M + H]^+$, 495.2 $[M + Na]^+$, 967.6 $[2M + Na]^+$; HRMS m/z calcd. for $C_{22}H_{32}O_{11}$: 473.2017, obsd: 473.2062.

***E*-4-(2-acetamido-3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-but-2-enoic acid *tert*-butyl ester (15).** Cross-metathesis of **4** (129 mg, 0.348 mmol) and *tert*-butyl acrylate (2 mmol) using the general procedure described above yielded **15** as a white solid (121 mg, 0.257 mmol, 74%, $E/Z = 20{:}1$): $[\alpha]_D^{20} = -19.2^\circ$ ($c = 0.5$, $CHCl_3$); IR (thin film) 2937, 1740, 1703, 1653, 1558, 1435, 1367, 1221, 1157, 1105, 1043, 988, 945, 901, 853, 818 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.83 (dt, $J_{2,3} = 15.7$, $J_{3,4a} = J_{3,4b} = 6.7$, 1H, H-3), 6.01 (d, $J_{NH,2'} = 9.5$, 1H, NH), 5.80 (d, 1H, H-2), 5.05 (m, 2H, H-3′and H-4′), 4.23 (dd, $J_{5',6a'} = 5.4$, $^2J_{6a',6b'} = 12.3$, 1H, H-6a′), 4.08 (dd, $J_{5',6b'} = 2.4$, 1H, H-6b′), 4.07 (m, 1H, H-2′), 3.63 (ddd, $J_{4',5'} = 7.8$, 1H, H-5′), 3.59 (ddd, $J_{1',2'} = 11.7$, $J_{1',4a} = 4.8$, $J_{1',4b} = 7.1$, 1H, H-1′), 2.46 (m, 2H, H-4a and H-4b), 2.08 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.93 (s, 3H, CH_3), 1.47 (s, 9H, *t*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 171.4, 170.6, 170.2, 169.2,

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165.6 (C═O, C-1), 142.7 (C-3), 125.0 (C-2), 80.2 (C_q *t*-Bu), 77.9 (C-1′), 75.5 (C-5′), 74.1 (C-4′), 68.6 (C-3′), 62.4 (C-6′), 53.7 (C-2′), 34.3 (C-4), 28.0 (CH_3 *t*-Bu), 23.0, 20.6, 20.5 (CH_3); ESI-MS (*m/z*): 417.2 $[M+H]^+$, 439.1 $[M+Na]^+$, 833.3 $[2M+H]^+$, 855.2 $[2M+Na]^+$; HRMS *m/z* calcd. for $C_{22}H_{33}NO_{10}$: 472.2177, obsd: 472.2218.

***E*-4-(2,3,4,6-tetra-*O*-acetyl-*α*-D-glucopyranosyl)-but-2-enoic acid (16).** Cross-metathesis of **1** (115 mg, 0.309 mmol) and acrylic acid (2 mmol) using the general procedure described above yielded **16** as a white solid (105 mg, 0.252 mmol, 82%, $E/Z = 10{:}1$): $[\alpha]_D^{20} = +68.0^\circ$ ($c = 0.2$, $CHCl_3$); IR (thin film) 2925, 1744, 1655, 1437, 1369, 1215, 1099, 1032, 982, 907 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.01 (dt, $J_{2,3} = 15.7$, $J_{3,4a} = J_{3,4b} = 7.0$, 1H, H-3), 5.98 (dt, $^4J_{2,4a} = {}^4J_{2,4b} = 1.5$, 1H, H-2), 5.32 (t, $J_{2',3'} = J_{3',4'} = 9.0$, 1H, H-3′), 5.11 (t, $J_{1',2'} = 5.5$, 1H, H-2′), 4.95 (t, 1H, $J_{4',5'} = 9.0$, H-4′), 4.37 (ddd, $J_{1',4a} = 10$, $J_{1',4b} = 4.4$, 1H, H-1′), 4.24 (dd, $J_{5',6a'} = 6.2$, $^2J_{6a',6b'} = 12.2$, 1H, H-6a′), 4.07 (dd, $J_{5',6b'} = 2.6$, 1H, H-6b′), 3.88 (ddd, 1H, H-5′), 2.74 (ddd, $^2J_{4a,4b} = 15.9$, 1H, H-4a), 2.74 (ddd, 1H, H-4a), 2.08 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 2.05 (s, 3H, CH_3), 2.04 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.9, 170.7, 169.8, 169.5, (C═O, C-1), 145.6 (C-3), 123.5 (C-2), 71.0 (C-1′), 69.9 (C-3′), 69.8 (C-2′), 69.4 (C-5′), 68.6 (C-4′), 62.1 (C-6′), 29.2 (C-4), 21.0, 20.63, 20.61, 20.5 (CH_3); ESI-MS (*m/z*): 417.2 $[M+H]^+$, 439.2 $[M+Na]^+$, 833.3 $[2M+H]^+$, 855.2 $[2M+Na]^+$; HRMS *m/z* calcd. for $C_{18}H_{24}O_{11}$: 417.1391, obsd: 417.1392.

***E*-4-(2-acetamido-3,4,6-tetra-*O*-acetyl-2-deoxy-*β*-D-glucopyranosyl)-but-2-enoic acid (17).** Cross-metathesis of **2** (134 mg, 0.361 mmol) and acrylic acid (2 mmol) using the general procedure described above yielded **17** as a white solid (122 mg, 0.292 mmol, 81%, $E/Z = 8{:}1$): $[\alpha]_D^{20} = +48.8^\circ$ ($c = 0.5$, $CHCl_3$); IR (thin film) 3292, 2926, 1740, 1655, 1537, 1433, 1373, 1229, 1090, 1034, 984, 914 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.24 (bs, 1H, COOH), 7.00 (dt, $J_{2,3} = 15.6$, $J_{3,4a} = J_{3,4b} = 7.0$, 1H, H-3), 6.23 (d, $J_{NH,2'} = 8.6$, 1H, NH), 5.94 (dt, $^4J_{2,4a} = {}^4J_{2,4b} = 1.5$, 1H, H-2), 5.00 (dd, $J_{2',3'} = 5.8$, $J_{3',4'} = 6.3$, 1H, H-3′), 4.90 (t, $J_{4',5'} = 5.8$, 1H, H-4′), 4.42 (dd, $J_{5',6a'} = 7.8$, $^2J_{6a',6b'} = 12.1$, 1H, H-6a′), 4.32 (m, 2H, H-1′ and H-2′), 4.09 (dd, $J_{5',6b'} = 3.9$, 1H, H-6b′), 3.97 (ddd, 1H, H-5′), 2.57 (dddd, $J_{1',4a} = 8.7$, 1H, H-4a), 2.43 (dddd, $J_{1',4b} = 4.0$, 1H, H-4b), 2.11 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.09 (s, 3H, CH_3), 2.01 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.8, 170.6, 170.21, 170.17, 168.9 (C═O, C-1), 145.9 (C-3), 123.3 (C-2), 71.4 (C-5′), 69.44 (C-1′), 69.38 (C-3′), 67.4 (C-4′), 61.0 (C-6′), 49.9 (C-2′), 31.0 (C-4), 23.1, 20.8, 20.7, 20.5 (CH_3); ESI-MS (*m/z*): 416.1 $[M+H]^+$, 438.0 $[M+Na]^+$, 831.4 $[2M+H]^+$, 853.3 $[2M+Na]^+$; HRMS *m/z* calcd. for $C_{18}H_{25}NO_{10}$: 416.1551, obsd: 416.1592.

***E*-4-(2,3,4,6-tetra-*O*-acetyl-*β*-D-glucopyranosyl)-but-2-enoic acid (18).** Cross-metathesis of **3** (162 mg, 0.435 mmol) and acrylic acid (2 mmol) using the general procedure described above yielded **18** as a white solid (141 mg,

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0.339 mmol, 78%, $E/Z = 10{:}1$): $[\alpha]_D^{20} = -7.6^\circ$ ($c = 1.0$, $CHCl_3$); IR (thin film) 2926, 1744, 1655, 1435, 1367, 1213, 1142, 1101, 1032, 980, 908, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.33 (bs, 1H, COOH), 7.03 (dt, $J_{2,3} = 15.7$, $J_{3,4a} = J_{3,4b} = 7.0$, 1H, H-3), 5.90 (dt, $^4J_{2,4a} = {}^4J_{2,4b} = 1.5$, 1H, H-2), 5.19 (t, $J_{2',3'} = J_{3',4'} = 9.5$, 1H, H-3′), 5.05 (t, $J_{4',5'} = 9.5$, 1H, H-4′), 4.92 (t, 1H, H-2′), 4.24 (dd, $J_{5',6a'} = 5.3$, $^2J_{6a',6b'} = 12.3$, 1H, H-6a′), 4.09 (dd, $J_{5',6b'} = 2.3$, 1H, H-6b′), 3.67 (ddd, 1H, H-5′), 3.59 (ddd, $J_{1',4a} = 4.8$, $J_{1',4b} = 7.1$, 1H, H-1′), 2.46 (m, 2H, H-4a and H-4b), 2.09 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.00 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 170.8, 170.7, 170.3, 169.6, 169.5 (C=O, C-1), 145.7 (C-3), 123.3 (C-2), 76.2 (C-1′), 75.7 (C-5′), 74.1 (C-3′), 71.7 (C-2′), 68.5 (C-4′), 62.1 (C-6′), 34.2 (C-4), 20.63, 20.59, 20.56, 20.54 (CH_3); ESI-MS (m/z): 417.2 $[M + H]^+$, 439.1 $[M + Na]^+$, 833.3 $[2M + H]^+$, 855.2 $[2M + Na]^+$; HRMS m/z calcd. for $C_{18}H_{24}O_{11}$: 417.1391, obsd: 417.1397.

***E*-4-(2-acetamido-3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-but-2-enoic acid (19).** Cross-metathesis of **4** (133 mg, 0.358 mmol) and acrylic acid (2 mmol) using the general procedure described above yielded **19** as a white solid (108 mg, 0.260 mmol, 72%, $E/Z = 19{:}1$): $[\alpha]_D^{20} = -21.0^\circ$ ($c = 0.2$, $CHCl_3$); IR (thin film) 2924, 2855, 1744, 1705, 1657, 1543, 1430, 1373, 1229, 1096, 1038, 980, 905 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.03 (dt, $J_{2,3} = 15.6$, $J_{3,4a} = J_{3,4b} = 7.0$, 1H, H-3), 6.90 (d, 1H, H-2), 5.81 (d, $J_{NH,2'} = 9.2$, 1H, NH), 5.07 (t, $J_{2',3'} = J_{3',4'} = 9.4$, 1H, H-3′), 5.03 (t, $J_{4',5'} = 9.4$, 1H, H-4′), 4.23 (dd, $J_{5',6a'} = 5.3$, $^2J_{6a',6b'} = 12.2$, 1H, H-6a′), 4.09 (dd, $J_{5',6b'} = 2.3$, 1H, H-6b′), 4.06 (app q, $J_{1',2'} = 9.4$, 1H, H-2′), 3.61 (ddd, 1H, H-5′), 3.43 (ddd, $J_{1',4a} = 4.0$, $J_{1',4b} = 7.8$, 1H, H-1′), 2.52 (m, 2H, H-4a and H-4b), 2.09 (s, 3H, CH_3), 2.04 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 1.95 (s, 3H, CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 172.8, 170.7, 170.3, 169.6, 169.5 (C=O, C-1), 147.2 (C-3), 123.3 (C-2), 78.0 (C-1′), 75.7 (C-5′), 74.2 (C-3′), 68.4 (C-4′), 62.1 (C-6′), 53.8 (C-2′), 34.2 (C-4), 23.1, 20.7, 20.6 (CH_3); ESI-MS (m/z): 427.3 $[M + H]^+$, 494.5 $[M + Na]^+$, 943.6 $[2M + H]^+$, 965.5 $[2M + Na]^+$; HRMS m/z calcd. for $C_{18}H_{25}NO_{10}$: 416.1551, obsd: 416.1614.

Cyanoethyl (2′,3′-dibenzoyl-uridin-5′-yl) vinylphosphonate (22). 1*H*-Tetrazole (84 mg, 1.2 mmol, 3 equiv.) was added to a solution of 2′,3′-dibenzoyl-uridine (180 mg, 0.398 mmol) and phosphine **21** (160 mg, 0.603 mmol, 2 equiv.) in dry acetonitrile (5 mL), under an argon atmosphere. After ^{31}P NMR showed complete disappearance of the starting material, the mixture was cooled (0°C) and *tert*-butyl-hydrogenperoxide (0.11 mL, 5.5 M in nonane) was added and allowed to react for 5 min. The mixture was diluted with ethyl acetate, washed with sat. aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. Silica gel column chromatography (ethyl acetate $\rightarrow$ 5% MeOH in ethyl acetate) afforded homogeneous **22** (172 mg, 0.289 mmol, 73%, 1:1 mixture of diastereoisomers) as a white solid: $[\alpha]_D^{20} = -61.6^\circ$ ($c = 0.5$, $CHCl_3$);

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IR (thin film) 2924, 2853, 1719, 1690, 1636, 1601, 1585, 1452, 1381, 1261, 1178, 1092, 1068, 1024, 1001, 906, 812, 727, 708 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 10.15 (bs, 1H, H-3), 7.98–7.79 (m, 4H, Bz), 7.67–7.11 (m, 7H, Bz and H-6), 6.64–6.02 (m, 4H, $CHCH_2$, and H-1′), 5.94–5.58 (m, 3H, H-5, H-2′ and H-3′), 4.64–4.19 (m, 4H, H-4′, H-5a′, H-5b′ and CH_2O CNE), 2.79 (t, $J = 6.0$, 2H, CH_2CN); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 165.2 (C═O Bz), 163.2 (C-4), 150.4 (C-2), 140.0 (C-6), 138.2 (CH_2 Vi), 133.6, 129.6, 128.1 (CH Bz), 128.0 (C Bz), 124.3 (CH Vi), 116.6 (CN), 103.4 (C-5), 87.5 (C-1′), 81.0 (C-4′), 73.2 (C-2′), 70.6 (C-3′), 64.9 (C-5′), 60.5 (CH_2O CNE), 19.7 (CH_2CN CNE); ^{31}P NMR (162 MHz, $CDCl_3$): δ 19.8, 19.5; ESI-MS (m/z): 596.2 $[M + H]^+$, 618.2 $[M + Na]^+$; HRMS m/z calcd. for $C_{28}H_{26}N_3O_{10}P$: 596.1492, obsd: 596.1503.

Cyanoethyl 2′,3′-dibenzoyl-uridin-5′-yl 3-(2-acetamido-3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranosyl)-propenylphosphonate (23). A mixture of Grubbs' second-generation precatalyst II (2.1 mg, 0.05 equiv.) and copper(I) chloride (1 mg, 0.20 equiv.) was added to a dry solution of vinylphosphonate 22 (50 μmol, 30 mg) and *C*-allyl-glycoside 2 (37 mg, 0.10 mmol, 2 equiv.) in DCM (1 mL) under an argon atmosphere. After refluxing for 3 hr, the mixture was concentrated and purified by silica gel column chromatography to yield 23 (27 mg, 29 μmol, 58%, $E/Z = 8{:}1$, 1:1 mixture of diastereoisomers). The *E*-isomer could be isolated by HPLC-purification: $[\alpha]_D^{20} = -48.0^\circ$ ($c = 0.1$, $CHCl_3$); IR (thin film) 2924, 2853, 1726, 1693, 1650, 1601, 1452, 1420, 1379, 1315, 1261, 1238, 1178, 1094, 1068, 1034, 1001, 810, 712 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.96 (m, 2H, Bz), 7.92 (m, 2H, Bz), 7.68 (m, 1H, H-6), 7.59 (m, 2H, Bz), 7.42 (m, 2H, Bz), 7.38 (m, 2H, Bz), 6.92 (m, 1H, H-2'), 6.25 (m, 1H, H-1′), 5.99 (m, 1H, H-1″), 5.89–5.80 (m, 2H, H-5 and H-3′), 5.75 (m, 1H, H-2′), 5.13 (m, 1H, H-6″), 4.94 (m, 1H, H-7″), 4.60 (m, 1H, H-4′), 4.46 (m, 2H, H-5a′ and H-5b′), 4.36 (m, 1H, H-9a″), 4.34–4.27 (m, 4H, H-4′, H-5″ and CH_2O CNE), 4.10 (m, 1H, H-9b″), 3.95 (m, 1H, H-8″), 2.87 (m, 2H, CH_2CN CNE), 2.76 (m, 1H, H-3a″), 2.51 (m, 1H, H-3b″), 2.10 (s, 3H, CH_3 AcO), 2.08 (s, 3H, CH_3 AcO), 2.08 (s, 3H, CH_3 AcO), 2.00 (s, 3H, CH_3 AcN); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 172.1, 171.7, 171.1, 170.3 (C═O Ac), 165.9 (C═O Bz), 164.7 (C-4), 152.2 (C-2″), 151.0 (C-2), 141.5 (C-6), 134.3, 130.1, 128.8 (CH Bz), 128.7 (C Bz), 117.9 (C-1″), 117.5 (CN), 103.5 (C-5), 88.2 (C-1′), 81.3 (C-4′), 73.9 (C-2′), 71.1 (C-3′), 71.0 (C-4″), 70.6 (C-8″), 70.1 (C-6″), 68.9 (C-7″), 65.2 (C-5′), 62.0 (C-9″), 61.3 (CH_2O CNE), 50.4 (C-5″), 31.1 (C-3″), 22.6 (CH_3 AcN), 20.8 (CH_3 AcO), 20.0 (CH_2CN CNE); ^{31}P NMR (162 MHz, $CDCl_3$): δ 20.2, 19.9; ESI-MS (m/z): 939.5 $[M + H]^+$, 1877.9 $[2M + H]^+$; HRMS m/z calcd. for $C_{43}H_{47}N_4O_{18}P$: 939.2403, obsd: 939.2696.

Uridin-5′-yl 3-(2-amino-2-deoxy-α-D-glucopyranosyl)-propenylphosphonate (24). Sodium methoxide (cat.) was added to a solution of phosphonate **23** (7 mg, 7.4 μmol) in MeOH (0.5 mL). After stirring for 16 hr, the mixture was neutralized (Dowex-H^+), filtered, and concentrated. Precipitation

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from MeOH/ether gave homogeneous **24** (3 mg, 5.4 μmol, 73%). ^{1}H NMR (400 MHz, MeOD): δ 7.82 (d, 1H, $J_{5,6} = 8.1$, H-6), 6.26 (ddt, 1H, $J_{2'',P} = 19.7$, $J_{2'',1''} = 16.9$, $J_{2'',3''} = 6.8$, H-2″), 5.76 (d, 1H, $J_{1',2'} = 4.8$, H-1′), 5.61 (dd, 1H, $J_{1'',P} = 18.4$, H-1″), 5.60 (d, 1H, H-5), 4.01 (dd, 1H, $J_{2',3'} = 5.2$, H-2′), 3.99 (dd, 1H, $J_{3',4'} = 3.0$, H-3′), 3.95 (dt, 1H, $J_{4'',5''} = 5.7$, $J_{3'',4''} = 4.2$, H-4″), 3.91–3.87 (m, 1H, H-4′), 3.83–3.71 (m, 2H, H-5′), 3.74 (dd, 1H, $J_{5'',6''} = 10.4$, H-5″), 3.55 (dd, 1H, $J_{9a'',9b''} = 11.9$, $J_{8'',9a''} = 2.7$, H-9a″), 3.47 (dd, 1H, $J_{8'',9b''} = 5.2$, H-9b″), 3.44 (dd, 1H, $J_{6'',7''} = 8.4$, H-6″), 3.25 (ddd, 1H, $J_{7'',8''} = 9.1$, H-8″), 3.13 (dd, 1H, H-7″), 2.46–2.34 (m, 1H, H-3a″), 2.16–2.07 (m, 1H, H-3″), 1.89 (s, 3H, NAc); ^{31}P NMR (162 MHz, $CDCl_3$): δ 14.5; ESI-MS (m/z): 552.1 $[M + H]^+$, 574.2 $[M + Na]^+$.

Dimethyl *E*-3-(2-acetamido-2-deoxy-α-D-glucopyranosyl)-propenylphosphonate (25). Deprotection of **9** as described for **23** gave **25** as a colorless oil (115 mg, 0.240 mmol, 95%): IR (thin film): 3393, 2912, 2853, 2359, 2341, 1635, 1558, 1456, 1188, 1036, 880 cm^{-1}; ^{1}H NMR (200 MHz, MeOD): δ 6.71 (m, 1H, H-2), 5.70 (m, 1H, H-1), 3.78–3.62 (m, 4H, OMe and H-4), 3.59–3.49 (m, 4H, OMe and H-5), 3.36–3.07 (m, 5H, H-6, H-7, H-8 and H-9), 2.53–2.28 (m, 2H, H-3), 1.89 (s, 3H, NAc); ^{13}C NMR (50.1 MHz, MeOD): δ 173.6 (CO Ac), 152.9 (C-2), 118.9 (C-1), 75.3, 73.6, 73.4, 72.2 (C-4, C-6, C-7, C-8), 63.2 (C-9), 53.7 (MeOP), 50.4 (C-5), 31.2 (C-3), 22.6 (CH_3 Ac); ESI-MS (m/z): 354.1 $[M + H]^+$, 376.2 $[M + Na]^+$, 707.4 $[2M + H]^+$, 729.4 $[2M + Na]^+$.

Dimethyl *E*-3-(2-acetamido-2-deoxy-β-D-glucopyranosyl)-propenylphosphonate (26). Deprotection of **11** as described for **23** gave **26** as a colorless oil (115 mg, 0.240 mmol, 95%): IR (thin film): 3391, 2359, 2338, 1636, 1558, 1188, 1038, 880 cm^{-1}; ^{1}H NMR (400 MHz, MeOD): δ 7.93 (d, 1H, $J_{NH,5} = 9.5$, NH), 6.85 (ddt, 1H, $J_{2,P} = 22.3$, $J_{1,2} = 17.2$, $J_{2,3} = 6.8$, H-2), 5.75 (ddt, 1H, $^2J_{1,P} = 22.2$, $J_{1,3} = 1.5$, H-1), 3.83 (dd, 1H, $^2J_{9a,9b} = 12.0$, $J_{8,9a} = 2.3$, H-9a), 3.71 (d, 3H, $J_{Me,P} = 11.2$, MeOP), 3.70 (d, 3H, $J_{Me,P} = 11.2$, MeOP), 3.63 (dd, 1H, $J_{8,9b} = 5.7$, H-9b), 3.62 (ddd, 1H, $J_{4,5} = 10.1$, $J_{5,6} = 9.8$, H-5), 3.39 (ddd, 1H, $J_{3a,4} = 3.8$, $J_{3b,4} = 7.2$, H-4), 3.37 (dd, 1H, $J_{6,7} = 8.6$, H-6), 3.28 (dd, 1H, $J_{7,8} = 9.8$, H-7), 2.55 (ddddd, 1H, $^4J_{3a,P} = 2.0$, $^2J_{3a,3b} = 15.2$, H-3a), 2.41 (ddddd, 1H, $^4J_{3b,P} = 2.5$, H-3a), 1.97 (s, 3H, CH_3 Ac); ^{13}C NMR (100 MHz, MeOD): δ 173.6 (CO Ac), 153.0 (C-2), 119.0 (C-1), 71.0, 70.6, 70.1, 68.9 (C-4, C-6, C-7, C-8), 62.8 (C-9), 54.8 (MeOP), 50.4 (C-5), 31.1 (C-3), 22.3 (CH_3 Ac); ESI-MS (m/z): 354.1 $[M + H]^+$, 376.2 $[M + Na]^+$, 707.4 $[2M + H]^+$, 729.4 $[2M + Na]^+$.

REFERENCES

[1] For reviews see: (a) Ivin, K.J.; Mol, J.C. *Olefin Metathesis and Olefin Metathesis Polymerization*, 1st Ed.; Academic Press: London, 1997; (b) Fürstner, A. Recent advancements in ring closing olefin metathesis. Top. Catal. **1997**, *4*, 285–299; (c) Schuster, M.; Blechert, S. Olefin metathesis in organic chemistry. Angew.

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Chem. Int. Ed. Engl. **1997**, *36*, 2037–2056; (d) Grubbs, R.H.; Chang, S. Recent advances in olefin metathesis and its application in organic synthesis. Tetrahedron **1998**, *54*, 4413–4450; (e) Armstrong, S.K. Ring closing diene metathesis in organic synthesis. J. Chem Soc.-Perkin Trans. 1, **1998**, 371–388; (f) Ivin, K.J. Some recent applications of olefin metathesis in organic synthesis: a review. J. Mol. Catal. A **1998**, *133*, 1–16; (g) Pandit, U.K.; Overkleeft, H.S.; Borer, B.C.; Bieräugel, H. Synthesis mediated by ring-closing metathesis—applications in the synthesis of azasugars and alkaloids. Eur. J. Org. Chem. **1999**, 959–968; (h) Wright, D.L. Application of olefin metathesis to organic synthesis. Curr. Org. Chem. **1999**, *3*, 211–240; (i) Blechert, S. Olefin metathesis—recent applications in synthesis. Pure Appl. Chem. **1999**, *71*, 1393–1399; (j) Jørgensen, P.; Hadwiger, P.; Madsen, R.; Stütz, A.E.; Wrodnigg, T.M. Olefin metathesis in carbohydrate chemistry. Curr. Org. Chem. **2000**, *4*, 565–588; (k) Roy, R.; Das, S.K. Recent applications of olefin metathesis and related reactions in carbohydrate chemistry. Chem. Commun. **2000**, 519–529; (l) Fürstner, A. Olefin metathesis and beyond. Angew. Chem. Int. Ed. **2000**, *39*, 3013–3043; (m) Hoveyda, A.H.; Schrock, R.R. Catalytic asymmetric olefin metathesis. Chem. Eur. J. **2001**, *7*, 945–950; (n) Schrock, R.R.; Hoveyda, A.H. Molybdenum and tungsten imido alkylidene complexes as efficient olefin-metathesis catalysts. Angew. Chem. Int. Ed. **2003**, *42*, 4592–4633; (o) Connon, S.J.; Blechert, S. Recent developments in olefin cross-metathesis. Angew. Chem. Int. Ed. **2003**, *42*, 1900–1923; (p) Leeuwenburgh, M.A.; Van der Marel, G.A.; Overkleeft, H.S. Olefin metathesis in glycobiology: new routes towards diverse neoglycoconjugates. Curr. Opin. Chem. Biol. **2003**, *7*, 757–765.

[2] Trnka, T.M.; Grubbs, R.H. The development of $L_2X_2Ru = CHR$ olefin metathesis catalysts: an organometallic success story. Acc. Chem. Res. **2001**, *34*, 18–29.

[3] Gibson, S.E.; Keen, S.P. Cross-metathesis. Top. Organomet. Chem. **1998** (155), 181 and ref 10.

[4] (a) Pietraszuk, C.; Fischer, H.; Kujawa, M.; Marciniec, B. Cross-metathesis of vinylsilanes with olefins in the presence of Grubbs' catalyst. Tetrahedron Lett. **2001**, *42*, 1175–1178; (b) Ahmed, M.; Arnauld, T.; Barret, A.G.M.; Braddock, D.C.; Flack, K.; Procopiou, P.A. Allene cross-metathesis: synthesis of 1,3-disubstituted allenes. Org. Lett. **2000**, *2*, 551–553; (c) Blackwell, H.E.; O'Leary, D.J.; Chatterjee, A.K.; Washenfelder, R.A.; Bussmann, D.A.; Grubbs, R.H. New approaches to olefin cross-metathesis. J. Am. Chem. Soc. **2000**, *122*, 58–71; (d) Seshadri, H.; Lovely, C.J. Application of olefin cross-metathesis to organometallics. Synthesis of unsaturated ferrocenyl alcohols and ketones. Org. Lett. **2000**, *2*, 327–330; (e) Hu, Y.J.; Roy, R. Cross-metathesis of N-alkenyl peptoids with O- or C-allyl glycosides. Tetrahedron Lett. **1999**, *40*, 3305–3308; (f) Biagini, S.C.G.; Gibson, S.E.; Keen, S.P. Cross-metathesis of unsaturated alpha-amino acid derivatives. J. Chem. Soc. Perkin Trans. 1 **1998**, 2485–2499.

[5] (a) Fürstner, A.; Thiel, O.R.; Lehmann, C.W. Study concerning the effects of chelation on the structure and catalytic activity of ruthenium carbene complexes. Organometallics **2002**, *21*, 331–335; (b) Jafarpour, L.; Hillier, A.C.; Nolan, S.P. Improved one-pot synthesis of second-generation ruthenium olefin metathesis catalysts. Organometallics **2002**, *21*, 442–444; (c) Scholl, M.; Trnka, T.M.; Morgan, J.P.; Grubbs, R.H. Increased ring closing metathesis activity of ruthenium-based olefin metathesis catalysts coordinated with imidazolin-2-ylidene ligands. Tetrahedron Lett. **1999**, *40*, 2247–2250.

[6] (a) Morgan, J.P.; Morrill, C.; Grubbs, R.H. Selective ring opening cross metathesis of cyclooctadiene and trisubstituted cycloolefins. Org. Lett. **2002**, *4*, 67–70; (b) Chatterjee, A.K.; Sanders, D.P.; Grubbs, R.H. Synthesis of symmetrical trisubstituted olefins by cross metathesis. Org. Lett. **2002**, *4*, 1939–1942; (c) Choi, T.L.; Chatterjee, A.K.; Grubbs, R.H. Synthesis of alpha,beta-unsaturated amides by

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olefin cross-metathesis. Angew. Chem. Int. Ed. **2001**, *40*, 1277; (d) Lera, M.; Hayes, C.J. An olefin cross-metathesis approach to vinylphosphonate-linked nucleic acids. Org. Lett. **2001**, *3*, 2765–2768; (e) Stragies, R.; Voigtmann, U.; Blechert, S. Improved yne-ene-cross metathesis utilizing a dihydroimidazole carbene ruthenium complex. Tetrahedron Lett. **2000**, *41*, 5465–5468; (f) Chatterjee, A.K.; Morgan, J.P.; Scholl, M.; Grubbs, R.H. Synthesis of functionalized olefins by cross and ring-closing metatheses. J. Am. Chem. Soc. **2000**, *122*, 3783–3784; (g) Morgan, J.P.; Grubbs, R.H. In situ preparation of a highly active N-heterocyclic carbene-coordinated olefin metathesis catalyst. Org. Lett. **2000**, *2*, 3153–3155; (h) Chatterjee, A.K.; Grubbs, R.H. Synthesis of trisubstituted alkenes via olefin cross-metathesis. Org. Lett. **1999**, *1*, 1751–1753.

[7] (a) Crowe, W.E.; Goldberg, D.R.; Zhang, Z.J. Preparation of allylsilanes via cross-metathesis. Tetrahedron Lett. **1996**, *37*, 2117–2120; (b) Schuster, M.; Lucas, N.; Blechert, S. Ruthenium-catalysed cross metathesis binding of functionalized olefins to polystyrene resin via a novel allylsilyl linker suitable for electrophilic cleavage. Chem. Commun. **1997**, 823–824.

[8] Brümmer, O.; Rückert, A.; Blechert, S. Olefin cross-metathesis with monosubstituted olefins. Chem. Eur. J. **1997**, *3*, 441–446.

[9] Blackwell, H.E.; O'Leary, D.J.; Chatterjee, A.K.; Washenfelder, R.A.; Bussmann, D.A.; Grubbs, R.H. New approaches to olefin cross-metathesis. J. Am. Chem. Soc. **2000**, *122*, 58–71.

[10] Chatterjee, A.K.; Choi, T.L.; Sanders, D.P.; Grubbs, R.H. A general model for selectivity in olefin cross metathesis. J. Am. Chem. Soc. **2003**, *125*, 11360–11370.

[11] Bennek, J.A.; Gray, G.R. An efficient synthesis of anhydroalditols and allyl c-glycosides. J. Org. Chem. **1987**, *52*, 892–897.

[12] Roe, B.A.; Boojamra, C.G.; Griggs, J.L.; Bertozzi, C.R. Synthesis of beta-C-glycosides of N-acetylglucosamine via Keck allylation directed by neighboring phthalimide groups. J. Org. Chem. **1996**, *61*, 6442–6445.

[13] Lewis, M.D.; Cha, J.K.; Kishi, Y. Highly stereoselective approaches to alpha-C-glycopyranoside and beta-C-glycopyranoside. J. Am. Chem. Soc. **1982**, *104*, 4976–4978.

[14] Fuchss, T.; Schmidt, R.R. Synthesis of the C-analog of 2-acetylamino-2-deoxy-beta-D-glucopyranosyl L- and D-serine. Synthesis **1998**, *5*, 753–758.

[15] (a) Timmer, M.S.M.; Ovaa, H.; Filippov, D.V.; Van der Marel, G.A.; Van Boom, J.H. An expeditious route to phosphorus heterocycles based on ring-closing metathesis. Tetrahedron Lett. **2000**, *41*, 8635–8638; (b) Timmer, M.S.M.; Ovaa, H.; Filippov, D.V.; Van der Marel, G.A.; Van Boom, J.H. Synthesis of phosphorus mono- and bicycles by catalytic ring-closing metathesis. Tetrahedron Lett. **2001**, *42*, 8231–8233.

[16] Rivard, M.; Blechert, S. Effective and inexpensive acrylonitrile cross-metathesis: utilisation of Grubbs II precatalyst in the presence of copper(I) chloride. Eur. J. Org. Chem. **2003**, 2225–2228.

[17] Van den Berg, R.J.B.H.N.; Donker-Koopman, W.; Van Boom, J.H.; Aerts, H.M.F.G.; Noort, D. Design and synthesis of 2-acetamidomethyl derivatives of isofagomine as potential inhibitors of human lysomal. Bioorg. Med. Chem. **2004**, *12*, 891–902.

[18] Lind, T.; Lindahl, U.; Lidholt, K. Biosynthesis of heparin heparan-sulfate—identification of a 70-kDa protein catalyzing both the D-glucuronosyltransferase and the N-acetyl-D-glucosaminyltransferase reactions. J. Biol. Chem. **1993**, *268*, 20705–20708.

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