Synthesis of Glycoporphyrins by Cross-Metathesis Reactions

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Abstract: An easy synthetic approach to glycoporphyrins from zinc(II)-2-vinyl-5,10,15,20-tetraphenylporphyrin or zinc(II)-protoporphyrin-IX dimethyl ester and *O*-allyl carbohydrate acetonides by cross-metathesis is reported.

Key words: vinylporphyrins, carbohydrate, cross-metathesis, Grubbs catalyst

Porphyrin and carbohydrate derivatives constitute two groups of natural compounds which play key roles in many vital functions of life.[1] It is anticipated that any attachment of sugar units to porphyrin macrocycles might give rise to derivatives which can be of great significance for medicinal and other applications.[1] Porphyrins with sugar moieties have not only better solubility in aqueous solutions, which is an important factor for their biodistribution, but also display specific membrane interactions that can affect the plasmatic lifetime of the drug.[2]

The olefin cross-metathesis (CM) has been an extremely useful synthetic coupling technique due to its mild reaction conditions and exceptional tolerance towards a variety of functional groups.[3] Recently, metathesis conditions have been utilized in porphyrin modifications using the first- (**1**) and second-generation (**2**) Grubbs catalysts (Figure 1).[4] To our knowledge only one of these studies has been concerned with the synthesis of a sugar derivative using the Grubbs first-generation catalyst.[4f]

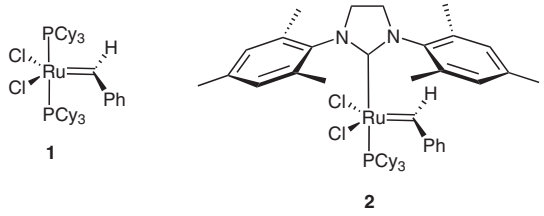

Figure 1 Grubbs' first- (**1**) and second-generation (**2**) catalysts

Our methodology leading to new β-substituted glycoporphyrins involves the reaction of vinylporphyrins (**3** and **4**) with allyl carbohydrate acetonides (**5a**–**e**) in the presence of the commercial available 'second-generation' Grubbs catalyst (**2**), in refluxing degassed dichloromethane under argon atmosphere. The reagents used were the Zn(II) complexes of 2-vinyl-5,10,15,20-tetraphenylporphyrin (**3**)[5] and protoporphyrin-IX dimethyl ester (**4**)[6] and the allylic acetonides[7] of the D-ribose (**5a**), D-galactose (**5b**), D-glucose (**5c**), and two isomeric derivatives of D-fructose (**5d** and **5e**, Scheme 1).

Table 1 Reactants, Products, and Yields of the Reactions

Entry	Vinylporphyrin	Allyl sugar	Product	Time (h)	Yield (%)
1	**3**	**5a**	**6a**	4	98
2	**3**	**5b**	**6b**	4	95
3	**3**	**5c**	**6c**	4	98
4	**3**	**5d**	**6d**	4	97
5	**3**	**5e**	**6e**	4	95
6	**4**	**5a**	**7a**	8	87
7	**4**	**5b**	**7b**	8	86
8	**4**	**5c**	**7c**	8	84
9	**4**	**5d**	**7d**	8	74
10	**4**	**5e**	**7e**	8	93

The reactions with vinylporphyrin **3** were carried out using equimolar amounts of the allyl sugars. In the case of the zinc(II) protoporphyrin-IX dimethyl ester (**4**) two equivalents of each carbohydrate were used. The reactions were monitored by TLC using a 8:2 mixture of toluene–ethyl acetate as the eluent. In all cases the Grubbs catalyst **2** was used in 25% mol. The yields of the reactions with vinylporphyrin **3** are almost quantitative while those involving porphyrin **4** are in the range of 74% to 93% (Table 1). The lower yields in the last set of reactions (entries 6–10), are probably due to the fact that the relation catalyst/double bond is only 12.5%. In all cases no products of dimerization of the porphyrins or the allyl carbohydrate acetonides were detected.

The products were isolated by flash chromatography using a gradient of toluene–ethyl acetate. All glycoporphyrin derivatives were characterized by 1D and 2D NMR techniques and by MALDI-TOF mass spectrometry. The NMR spectra show, in all cases, that only *E*-isomers are formed. The high *E*-stereoselectivity can be rationalized by the steric hindrance provided by the large tetrapyrrolic

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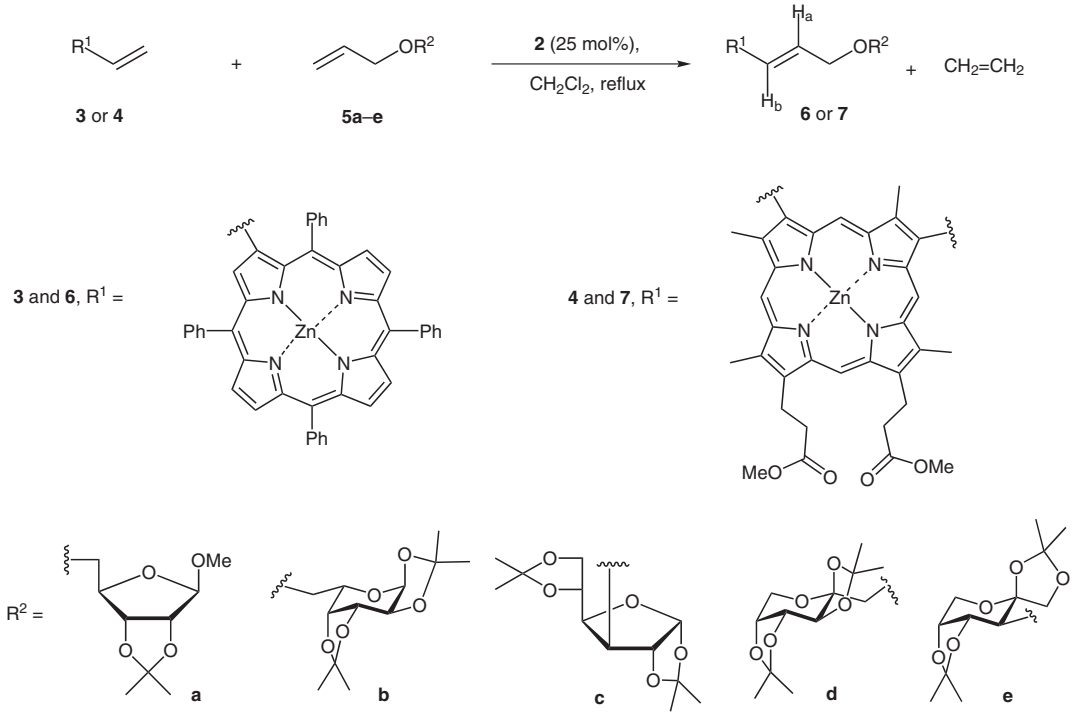

Scheme 1 Cross-metathesis between vinylporphyrins and allyl sugars

macrocycle and the carbohydrate moiety.[8] For example, the ^{1}H NMR spectrum of the ribose derivative **6a** shows a coupling constant of 15.6 Hz for the signals of the vinylic protons Ha (a double triplet at δ = 6.30 ppm) and Hb (a doublet at δ = 6.20 ppm). This provides a clear evidence for *E*-stereoselectivity. The ^{1}H NMR spectra of the other glycoporphyrins **6** follow this pattern.

The presence of two vinyl groups in the structure of zinc(II) protoporphyrin-IX dimethyl ester (**4**) allows the synthesis of glycoporphyrins containing two sugar units (**7a**–**e**).

The ^{1}H NMR spectrum of the glycoprotoporphyrin-IX **7a** shows that two carbohydrate moieties are attached. The coupling constants of 17.5 Hz for the resonances of protons Ha (double triplets at δ = 6.11 and 6.12 ppm) and Hb (doublets at δ = 6.23 and 6.24 ppm) confirm the formation of the product with *E*-stereoselectivity at both vinyl groups. We also observed the formation of porphyrinic derivatives **7b**–**e** with *E*-stereochemistry.

Treatment of dichloromethane solutions of **6a** and **7a** with trifluoroacetic acid (15 min at r.t.), followed by the addition of water, resulted in quantitative demetalation and removal of the isopropylidene groups. The ^{1}H NMR spectra of the anomeric mixtures obtained show the signals of the uncomplexed porphyrin inner protons at δ = –2.70 and –4.16 ppm, respectively, for **6a** and **7a**, and the disappearance of the signals corresponding to the isopropylidene groups.

In summary, this methodology provides a useful new approach to glycoporphyrins.[9] This work demonstrates that the Grubbs catalyst **2** efficiently catalyzes the cross-metathesis of vinyl-metalloporphyrins **3** and **4** with allyl carbohydrate templates in stoichiometric relations.

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(9) **General Procedure for Glycoporphyrins (6 and 7)**

A solution of the metalloporphyrin (0.04 mmol) and Grubbs catalyst **2** (25% mol, 0.01 mmol) in degassed dry CH_2Cl_2 (2 mL) was heated at reflux, under argon, and the allyl sugar **5**, dissolved in CH_2Cl_2 (1 mL), was immediately added by a syringe to the mixture. The reflux was kept as mentioned in Table 1. The solvent was evaporated and the residue was purified by flash chromatography using a gradient of toluene–EtOAc as the eluent. The products **6** and **7** were obtained as red solids after crystallization from PE.

Selected Data for 6a

Mp 171–172 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.30 (s, 3 H, CH_3), 1.47 (s, 3 H, CH_3), 3.27 (s, 3 H, OCH_3), 3.27 (dd, *J* = 8.3 and 9.7 Hz, 1 H, H-5′a), 3.47 (dd, *J* = 6.3 and 9.7 Hz, 1 H, H-5′b), 3.87 (dd, *J* = 2.1 and 5.9 Hz, 2 H, C*H*$_2$CH=CH), 4.22 (dd, *J* = 6.3 and 8.3 Hz, 1 H, H-4′), 4.52 (d, *J* = 5.9 Hz, 1 H, H-2′), 4.59 (d, *J* = 5.9 Hz, 1 H, H-3′), 4.86 (s, 1 H, H-1′), 6.20 (d, *J* = 15.6 Hz, 1 H, Hb), 6.30 (dt, *J* = 5.9 and 15.6 Hz, 1 H, Ha), 7.66–7.79 (m, 12 H, ArH), 8.05–8.22 (m, 8 H, Ar *ortho*), 8.81–8.94 (m, 6 H, H-7, H-8, H-12, H-13, H-17, H-18), 8.95 (d, *J* = 0.8 Hz, 1 H, H-3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.9 (CH_3), 26.4 (CH_3), 54.7 (OCH_3), 70.4 (C-5), 72.2 (*C*H_2CH=CH), 81.9 (C-3), 84.7 (C-2), 85.0 (C-4), 109.0 (C-1), 112.2 (C-6), 120.5, 121.0, 121.5, 126.5, 126.6, 126.7, 127.3, 127.4, 127.5, 127.8, 129.5 (C-a), 130.9, 131.5, 131.9, 132.0, 132.1, 132.2, 133.8 (C-b), 133.8, 133.9, 134.3, 142.7, 142.9, 146.7, 150.2, 150.3, 150.4, 150.7. UV/Vis ($CHCl_3$): λ_{max} (log ε) = 429 (4.57), 559 (4.28), 596.5 (3.63). HRMS (MALDI-TOF): *m/z* calcd for $C_{56}H_{46}N_4O_5Zn$ $[M]^+$: 918.2760; found: 918.2739.

Selected Data for 6b

Mp 165–166 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.48 (s, 3 H, CH_3), 1.51 (s, 3 H, CH_3), 3.60 (dd, *J* = 6.7 and 10.1 Hz, 1 H, H-6′a), 3.68 (dd, *J* = 6.7 and 10.1 Hz, 1 H, H-6′b), 3.93–4.05 (m, 1 H, H-5′), 3.93–4.05 (m, 2 H, C*H*R$_{2R}$CH=CH), 4.31 (dd, *J* = 1.9 and 8.0 Hz, 1 H, H-4′), 4.32 (dd, *J* = 2.5 and 5.0 Hz, 1 H, H-2′), 4.62 (dd, *J* = 2.5 and 8.0 Hz, 1 H, H-3′), 5.56 (d, *J* = 5.0 Hz, 1 H, H-1′), 6.22 (d, *J* = 15.5 Hz, 1 H, Hb), 6.41 (dt, *J* = 6.3 and 15.5 Hz, 1 H, Ha), 7.68–7.81 (m, 12 H, ArH), 8.06–8.22 (m, 8 H, Ar *ortho*), 8.82–8.94 (m, 6 H, H-7, H-8, H-12, H-13, H-17, H-18), 8.96 (s, 1 H, H-3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 24.5 (CH_3), 26.9 (CH_3), 26.1 (CH_3), 66.8 (C-5), 68.9 (C-6), 70.6 (C-2), 70.7 (C-3), 71.2 (C-4), 72.8 (*C*H_2CH=CH), 96.4 (C-1), 108.5 (C-8), 109.2 (C-7), 120.9, 121.2, 121.5, 126.5, 126.9, 127.4, 127.5, 127.9, 129.5 (C-a), 129.7, 131.0, 131.5, 131.9, 132.0, 132.1, 132.3, 133.9 (C-b), 134.4, 142.8, 142.9, 142.7, 143.1, 146.7, 148.6, 150.0, 150.1, 150.2, 150.3, 150.5, 150.8. UV/Vis ($CHCl_3$): λ_{max} (log ε) = 429 (4.55), 558.5 (4.25), 599.5 (3.62). HRMS (MALDI-TOF): *m/z* calcd for $C_{59}H_{50}N_4O_6Zn$ $[M]^+$: 974.3022; found: 974.3006.

Selected Data for 6c

Mp 190–191 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.32 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.38 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 4.06–4.11 (m, 1 H, H-6′a), 4.06–4.11 (m, 1 H, H-6′b), 4.06–4.11 (m, 2 H, C*H*$_2$CH=CH), 4.06–4.11 (m, 1 H, H-3′), 4.16 (dd, *J* = 2.9 and 7.6 Hz, 1 H, H-4′), 4.30–4.37 (m, 1 H, H-5′), 4.59 (d, *J* = 3.7 Hz, 1 H, H-2′), 5.93 (d, *J* = 3.7 Hz, 1 H, H-1′), 6.26 (d, *J* = 15.6 Hz, 1 H, Hb), 6.36 (dt, *J* = 5.9 and 15.6 Hz, 1 H, Ha), 7.69–7.80 (m, 12 H, ArH), 8.07–8.21 (m, 8 H, Ar *ortho*), 8.82–8.93 (m, 6 H, H-7, H-8, H-12, H-13, H-17, H-18), 8.94 (s, 1 H, H-3). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 25.4 (CH_3), 26.3 (CH_3), 26.8 (CH_3), 26.9 (CH_3), 67.2 (C-6), 72.5 (C-5), 81.1 (C-4), 81.2 (C-3), 82.9 (C-2), 105.3 (C-1), 108.8 (C-8), 111.8 (C-7), 120.5, 121.1, 126.6, 126.8, 126.9, 127.1, 127.5, 127.6, 127.9, 129.7 (C-a), 130.1, 131.6, 131.9, 132.0, 132.1, 132.3, 133.9, 134.0 (C-b), 134.3, 134.4, 142.7, 142.9, 148.4, 150.1, 150.2, 150.3, 150.8. UV/Vis ($CHCl_3$): λ_{max} (log ε) = 429 (4.55), 558.5 (4.26), 595.5 (3.59). HRMS (MALDI-TOF): *m/z* calcd for $C_{59}H_{50}N_4O_6Zn$ $[M]^+$: 974.3022; found: 974.3014.

Selected Data for 7a

Mp 115–116 °C. ^{1}H NMR (300.13 MHz, $CDCl_3$): δ = 1.10 (s, 3 H, CH_3), 1.17 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.40 (s, 3 H, CH_3), 1.41 (s, 3 H, CH_3), 2.94–3.04 (m, 2 H, CH_2), 3.37 (s, 3 H, CH_3), 3.38 (s, 3 H, CH_3), 3.44 (s, 3 H, CH_3), 3.45 (s, 3 H, CH_3), 3.61 (s, 3 H, OCH_3), 3.61–3.89 (m, 4 H, H-5′), 3.62 (s, 3 H, OCH_3), 3.64 (s, 3 H, OCH_3), 3.74–3.90 (m, 2 H, CH_2), 3.74–3.90 (m, 2 H, C*H*$_2$CH=CH), 3.99–4.14 (m, 4 H, CH_2), 4.57 (d, *J* = 5.9 Hz, 1 H, H-2′) and 4.62 (d, *J* = 5.9 Hz, 1 H, H-2′), 4.67–4.73 (m, 2 H, H-4′), 4.91 (d, *J* = 5.9 Hz, 1 H, H-3′) and 4.93 (d, *J* = 5.9 Hz, 1 H, H-3′), 5.04 (s, 1 H, H-1′) and 5.06 (s, 1 H, H-1′), 6.12 (dt, *J* = 5.9 and 17.5 Hz, 1 H, Ha) and 6.11 (dt, *J* = 5.9 and 17.5 Hz, 1 H, Ha), 6.24 (d, *J* = 17.5 Hz, 1 H, Ha) and 6.23 (d, *J* = 17.5 Hz, 1 H, Ha), 9.30 (s, 1 H, H$_{meso}$), 9.26 (s, 1 H, H$_{meso}$), 9.17 (s, 1 H, H$_{meso}$), 9.11 (s, 1 H, H$_{meso}$). ^{13}C NMR (75.47 MHz, $CDCl_3$): δ = 11.4, 11.5, 12.4 and 12.5 (4 × CH_3), 21.6 (CH_2), 24.9 and 26.4 (CH_3 of isopropylidene), 36.8 (CH_2), 51.6 (CO_2OCH_3), 54.7 and 54.8 (OCH_3), 71.1 (C-5′), 76.6 (*C*H_2CH=CH), 77.4 (C-4′), 82.1 (C-5′), 85.0 and 85.1 (C-2′), 95.4, 96.5, 97.9 and 97.2 (CH in 5, 10, 15, 20 positions), 109.2 and 109.3 (C-1′), 112.3 (C-6′), 119.0 and 119.1, 129.2, 130.3 and 130.5, 135.3, 135.9, 136.0, 136.1, 136.4, 137.8, 138.0, 144.9, 145.6, 145.7, 145.9, 146.0, 146.1, 146.2, 146.4, 147.0, 147.1, 173.3 (C=O). UV/Vis ($CHCl_3$): λ_{max} (log ε) = 415.5 (5.36), 544 (4.20), 580.5 (4.28). HRMS (MALDI-TOF): *m/z* calcd for $C_{56}H_{68}N_4O_{14}Zn$ $[M]^+$: 1084.4023; found: 1084.4007.