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The preparation of *C*-glycosyl amino acids—an examination of olefin cross-metathesis

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Abstract—A study investigating the structural features directing olefin cross-metathesis to afford *C*-glycoamino acids was carried out. These results lead to an appreciation of the importance of proximal functionality to the relative reactivity of olefins in metathesis reactions providing a variable that is useful to suppress undesirable self-metathesis.

Studies to understand the roles of glycoconjugates in biological regulation continue to define one of the important frontiers of molecular biology.[1] We have previously reported on our efforts to prepare stable analogs of *N*- and *O*-glycopeptides that may prove useful in biological studies to understand the relationship between oligosaccharide structure and disease and to provide potentially useful therapeutic agents.[2] The key to this approach lies in an effective olefin cross-metathesis reaction between an unnatural olefinic α-amino acid and an unsaturated *C*-glycoside (Fig. 1).

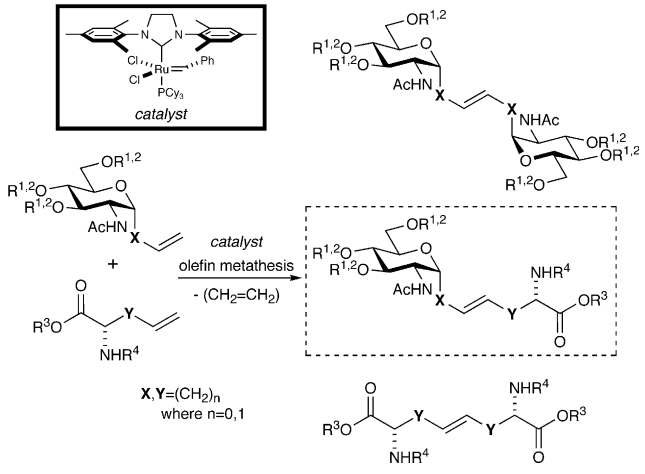

Figure 1. Olefin cross-metathesis to *C*-glycoamino acids.

Olefin cross-metathesis has emerged as an extraordinarily powerful method for fusing highly functionalized reaction partners.[3] The functional group tolerance of this method is particularly attractive for the present application of carbohydrate fusion to amino acids.[4] The challenges associated with cross-metathesis are well documented and are illustrated for the present case in Figure 1.[5] It can be seen that the desired cross-metathesis product (boxed) is but one of three products available as two self-metathesis products are also possible. The course of the metathesis reaction is controlled by several variables, including the reactivity of the various olefins in a reaction mixture that includes up to two

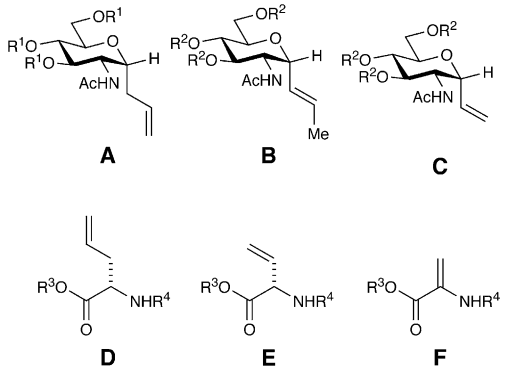

Figure 2. Substrates used in the metathesis study.

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starting olefins and three product olefins.[6] Furthermore, since the metathesis reaction is well known to be a reversible reaction, the stability of the products to the reaction conditions needs to be considered. In an effort to understand and optimize the cross-metathesis reaction leading to mucin *C*-glycoamino acids, a study was undertaken to examine the relative reactivity of these various components with respect to each other. It was a goal of these studies to gain insight to what structural features favored the desired course of the reaction in an effort to minimize the unwanted self-metathesis.

With this in mind, we chose to examine a series of substrates that would explore the variables of olefin substitution and proximal functionality[7] (Fig. 2). Using the methodology, we have previously disclosed, *C*-aminoglycoside substrates **A**–**C** were made available.[8] In addition to commercially available dihydroalanine **F**, allyl and

Table 1. Olefin metathesis study[a]

	A	B	C	D	E
A	**1a** (78%) **1b** (81%)	**2a** (84%) **2b** (82%) **2c** (80%)	NA	**6a** (74%) **6b** (78%) **6c** (70%) **6d** (60%) **6e** (70%)	**8** (80%)
B	**2a** (84%) **2b** (82%) **2c** (80%)	**3** (trace) + **2b** (47%)	NA	**7a** (82%) **7b** (77%) **7c** (69%) **7d** (77%) **7e** (62%)	**9** (none)
C	NA	NA	**3** (none)	**7e** (77%)	**9** (none)
D	**6a** (74%) **6b** (78%) **6c** (70%) **6d** (60%) **6e** (70%)	**7a** (82%) **7b** (77%) **7c** (69%) **7d** (77%) **7e** (62%)	**7e** (77%)	**4a** (76%) **4b** (86%)	NA
E	**8** (80%)	**9** (none)	**9** (none)	NA	**5** (<5%)

1a: R^1=Bn
1b: R^1=Ac

4a: R^3=Me, R^4=Boc
4b: R^3=Me, R^4=Fmoc

7a: R^1=Bn, R^3=Me, R^4=Fmoc
7b: R^1=Bn, R^3=Me, R^4=Boc
7c: R^1=Ac, R^3=Me, R^4=Fmoc
7d: R^1=Ac, R^3=Me, R^4=Boc
7e: R^1=Ac, R^3=Bn, R^4=CBz

2a: R^1=R^2=Bn
2b: R^1=R^2=Ac
2c: R^1=Ac, R^2=Bn

5

8

3

6a: R^1=Bn, R^3=Me, R^4=Fmoc
6b: R^1=Bn, R^3=Me, R^4=Boc
6c: R^1=Ac, R^3=Me, R^4=Fmoc
6d: R^1=Ac, R^3=Me, R^4=Boc
6e: R^1=Ac, R^3=Bn, R^4=CBz

9

[a] NA = not attempted.

vinyl glycines, **D** and **E**, were prepared using the methods reported by Myers[9] and Hanessian,[10] respectively.

With these substrates in hand, an examination of the possible cross- and self-metatheses using Grubbs' second generation catalyst (Fig. 1) was carried out with the results summarized in Table 1. Our initial focus was on cross-metathesis reactions, examining combinations of *C*-glycosides **A**–**C** with two equivalents of unnatural amino acids **D**–**F** to give the results indicated in the dashed boxes.[11] It was found that allyl glycine **D** was an effective reaction partner for all three *C*-glycosides, giving the various cross-metathesis products **6** and **7** in good yields. It is noteworthy that reaction times leading to the benzyl protected products (**6a**,**b** and **7a**,**b**) and acetate protected products (**6c**–**e** and **7c**–**e**) were 24 and 48 h, respectively, indicating a significant functional group effect on reactivity. In contrast to the allyl amino acids, vinyl glycine **E** was found to be reactive with only allyl *C*-glycoside **A** to afford cross-product **8**. Unfortunately, attempts to access the linker length corresponding to natural glycoamino acids, **9**, proved unsuccessful as vinylic *C*-glycosides **B** and **C** were unreactive with **E**. In agreement with previous reports, dehydroalanine **F** was found to be unreactive with both allyl and vinylic *C*-glycosides.[12,13]

Our attention was next turned toward reactions of self-metathesis. As was the case in cross-metathesis, the allyl substrates were found to be reactive with *C*-glycosides **A** and allylglycines **D** smoothly self-condensing to afford products **1** and **4**, respectively, in good yields. Perhaps not surprising, self-metathesis of vinylic substrates **B**, **C**, and **E** proved difficult, affording only trace amounts of the predicted products. It is particularly noteworthy that self-metathesis of **B** led not to the expected product **3** but, rather, to its homolog, **2b**, in 47% yield. The product was confirmed by carrying out the cross-metathesis of allyl and propenyl *C*-glycosides **A** and **B**, respectively, to afford good yields of products **2a** and **b**. The self-condensation of **B** vividly illustrates the reluctance of propenyl species to self-condense, preferring in this instance to undergo precedented double bond isomerization[14] to allow allyl-propenyl metathesis to afford **2b**, a cross-metathesis product (Fig. 3).

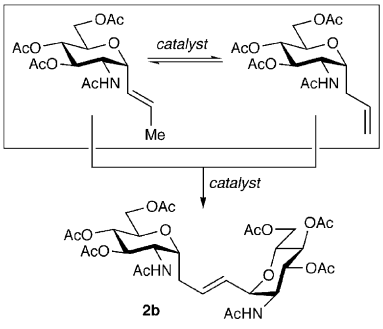

Figure 3. 'Self'-metathesis of the *C*-propenyl glycoside.

Additional insight into the cross-metathesis of **A** (R^1 = Bn) with **D** (R^3 = Me, R^4 = Fmoc) was obtained by following the course of the reaction by NMR. It was observed that the allylglycine was consumed within the first 2.5 h of the reaction with corresponding appearance of the homometathesis product **4b**. As the reaction proceeds, it was apparent that the disappearance of the allyl *C*-glycoside coincides with the disappearance of dimer **4b**, and the formation of the desired cross-product **6c**. This reaction follows the path shown in Figure 4 wherein the amino acid dimerizes prior to engaging the *C*-glycoside to afford the cross-product. This reaction falls into the selective cross-metathesis of a type I olefin with a type II olefin, as defined by Grubbs and co-workers.[6] Additional support for this reaction pathway was obtained when it was confirmed that independently prepared olefin **4b** participates in metathesis with *C*-allyl glycoside **A** (R^1 = Bn) to afford the expected cross-product **6c.**

The data shown (Table 1) lend insight to what structural features affect the course of these metathesis reactions. Figure 5 highlights the features deemed relevant in the present examples—the positioning of adjacent functionality (linked by bold bonds) and substitution of the (shaded) olefin. It was noted that reactions of mono- and disubstituted olefins **B** and **C** with allylic substrates (**A** and **D**) were sufficiently similar to suggest that olefin substitution is not the principle determinant in these metathesis reactions. This contrasts significantly with the poor reactivity of **B** and **C** with themselves or with vinyl glycines **E**, suggesting that the determining structural feature guiding these metathesis reactions is not olefin substitution, but rather the proximity of basic functionality to the olefin, perhaps contributing to the deactivation of the catalyst. Consistent with this, the

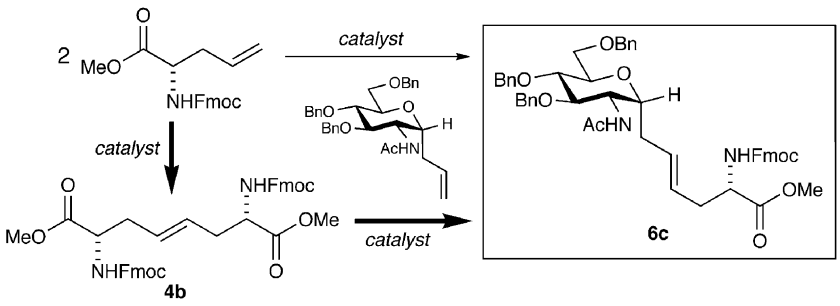

Figure 4. The allyl glycine/*C*-allyl glucosamine reaction pathway.

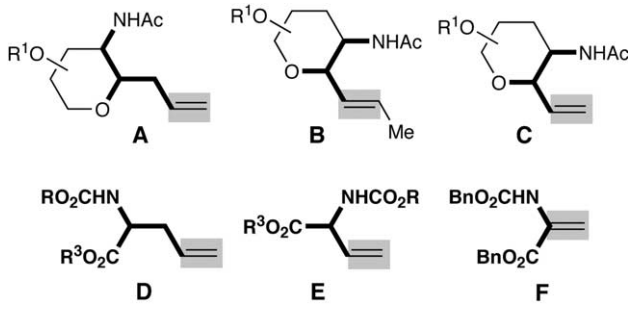

Figure 5. Important influences of olefin metathesis reactivity.

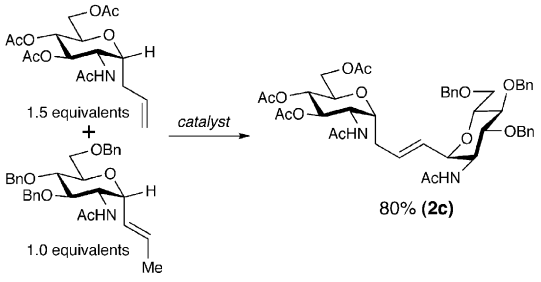

Figure 6. Proximal functionality favoring cross-metathesis.

allylic substrates, **A** and **D**, readily self-metathesize and show general reactivity toward cross-metathesis.

The notion that metathesis can be adjusted to favor the cross-product by distal functionality is rather remarkably demonstrated by the reaction of 1.5 equiv of **A** (R^1 = Ac) with 1.0 equiv of **B** (R^2 = Bn) to afford an 80% yield of the cross-product **2c** (Fig. 6). This result is clearly well beyond what would be expected for a statistical combination of these substrates and demonstrates how effective cross-coupling can be attained with appropriate adjustment of substrate functionality.

The results of this study emphasize the significant role that attendant functionality plays in guiding the course of olefin cross metathesis. In the present case, proximal functionality was found to be an important influence in guiding olefin metathesis to form the desired *C*-glycoamino acid cross-products. Of particular significance is the influence of proximal functionality in adjusting the relative reactivity of olefins to promote the desired pattern of reactivity. Efforts to exploit this observation are currently underway and will be reported in due course.

Acknowledgements

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11. Unless otherwise noted, all cross-metathesis reactions were allowed to proceed until consumption of the starting *C*-glycoside was noted by TLC analysis. For the instances where R^1, R^2 = Bn, 10 mol % of catalyst was used, whereas 20 mol % of catalyst was required for R^1, R^2 = OAc (see Table 1).
12. Selected spectral and physical data: Compound **1a**: mp = 190 °C (decomp.) IR (film, NaCl) 3319, 3039, 2908, 2855, 1649, 1554, 1457, 1379, 1099, 750, 706 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.82 (s, 6H), 2.14 (m, 4H), 3.58 (m, 2H), 3.78 (m, 10H), 4.19 (m, 2H), 4.51 (m, 12H), 5.84 (m, 2H), 6.44 (m, 2H), 7.29 (m, 30H). ^{13}C NMR ($CDCl_3$) δ 23.3, 29.5, 29.7, 34.6, 47.4, 67.9, 68.2, 71.8, 72.0, 73.2, 74.4, 74.9, 127.1, 127.6, 127.7, 127.8, 128.0, 128.3, 128.5, 137.4, 137.7, 138.2, 169.6. HRMS Calcd for $C_{62}H_{70}N_2O_{10}$ (MH^+): 1002.5030. Found: 1002.5002. Compound **1b**: R_f = 0.16 (70% acetone/hexanes) mp = 210 °C (decomposition) IR (film, NaCl) 3301, 2942, 2885, 1754, 1667, 1554, 1449, 1379, 1239, 1039, 924, 741 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.97 (s, 6H), 2.07 (s, 6H), 2.08 (s, 6H), 2.09 (s, 6H), 2.28 (m, 4H), 3.88 (m, 2H), 4.12 (m, 4H), 4.24 (m, 2H), 4.36 (dd, J = 6.0, 7.2 Hz, 2H), 4.99 (m, 4H), 5.46 (m, 2H), 5.92 (d, J = 9.0 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 20.7, 20.8, 23.2, 31.2, 50.0, 61.3, 67.6, 69.7, 70.8, 70.9, 127.9, 168.9, 169.6, 170.6, 170.8. HRMS Calcd for $C_{32}H_{46}N_2O_{16}$ (MH^+): 714.2847. Found: 714.2857. Compound **2b**: R_f = 0.29 (60% acetone/pet. ether) IR (film, NaCl) 3301, 3021, 2943, 1754, 1676, 1546, 1440, 1379, 1239, 1047, 767 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.90 (s, 3H), 1.94 (s, 3H), 1.95 (s, 3H), 1.99 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 2.08 (s, 3H), 2.34 (m, 2H), 3.91 (m, 2H), 4.26 (m, 5H), 4.35 (m, 1H), 4.44 (dd, J = 6.3, 12.0 Hz, 1H), 4.55 (m, 1H), 4.91 (m, 2H), 5.02 (m, 2H), 5.74 (m, 2H), 6.01 (d, J = 8.7 Hz, 1H), 6.06 (d, J = 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 20.6, 20.7, 20.8, 23.0, 23.1, 23.2, 31.2, 49.5, 50.9, 60.9, 62.2, 67.6, 68.6, 69.3, 69.9, 70.2, 70.7, 71.4, 73.9, 125.0, 133.2, 168.8, 168.1, 169.7, 169.9, 170.4, 170.7, 171.2. Compound **2c**: R_f = 0.31 (50% acetone/pet. ether) IR (film, NaCl) 3301, 3039, 2943, 1754, 1667, 1553, 1457, 1379, 1248, 1055, 767, 706 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.84 (s, 3H), 1.92 (s, 3H), 2.01 (s, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 2.22 (m, 1H), 2.37 (m, 1H), 3.58 (t, J = 3.3 Hz, 1H), 3.73 (m, 2H), 3.89 (m, 1H), 4.10 (m, 2H), 4.22 (m, 2H), 4.37 (dd, J = 6.3, 12.0 Hz, 1H), 4.44 (m, 1H), 4.58 (m, 2H), 4.91 (t, J = 6.0 Hz, 1H), 5.04 (m, 1H), 5.48 (dd, J = 5.0, 15.0 Hz, 1H), 5.70 (m, 1H),

5.97 (d, J = 8.7 Hz, 1H), 6.59 (d, J = 9.6 Hz, 1H), 7.27 (m, 21H). ^{13}C NMR ($CDCl_3$) δ 20.6, 20.7, 23.2, 31.2, 48.9, 51.4, 61.2, 62.3, 67.7, 67.9, 68.5, 69.1, 69.6, 69.8, 70.6, 71.1, 71.2, 72.4, 72.6, 73.2, 73.9, 74.4, 74.8, 75.2, 127.5, 127.6, 127.8, 127.9, 128.1, 128.3, 128.4, 129.3, 135.3, 137.4, 137.7, 138.0, 168.9, 169.7, 169.9, 170.6, 170.7. HRMS Calcd for $C_{46}H_{56}N_2O_{13}$ (MH^+): 844.3782. Found: 844.3783. Compound **4a**: R_f = 0.37 (70% EtOAc/pet. ether) IR (film, NaCl) 3371, 2978, 2934, 1719, 1519, 1449, 1379, 1256, 1178, 1064, 1029, 741 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18H), 2.44 (m, 4H), 3.73 (s, 6H), 4.31 (m, 2H), 5.09 (d, J = 7.7, 2H), 5.39 (m, 2H). ^{13}C NMR ($CDCl_3$) 28.7, 36.1, 52.8, 53.5, 80.4, 128.9, 155.6, 172.9. HRMS Calcd for $C_{20}H_{34}N_2O_8$ (MH^+): 430.2315. Found: 430.2317. Compound **4b**: R_f = 0.28 (60% EtOAc/pet. ether) IR (film, NaCl) 3354, 3048, 2952, 1720, 1527, 1457, 1352, 1221, 1064, 924, 750 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.52 (m, 4H), 3.75 (s, 6H), 4.21 (m, 2H), 4.44 (m, 6H), 5.44 (m, 2H), 5.53 (d, J = 8.1 Hz, 2H), 7.30 (m, 4H), 7.40 (t, J = 7.2 Hz, 4H), 7.61 (m, 4H), 7.76 (d, J = 7.5 Hz, 4H). ^{13}C NMR ($CDCl_3$) δ 35.4, 47.1, 52.5, 53.4, 67.0, 119.9, 125.0, 127.0, 127.7, 128.5, 141.2, 143.7, 155.7, 172.0. HRMS Calcd for $C_{40}H_{38}N_2O_8$ (MH^+): 674.2628 Found: 674.2609. Compound **6e**: R_f = 0.27 (75% EtOAc/pet. ether) IR (film, NaCl) 3345, 3039, 2952, 1754, 1676, 1545, 1379, 1248, 1055, 741, 706 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.95 (s, 3H), 2.01 (s, 2H), 2.02 (s, 3H), 2.05 (s, 3H), 2.24 (m, 2H), 2.47 (m, 2H), 3.80 (m, 1H), 4.08 (m, 2H), 4.22 (m, 1H), 4.33 (m, 1H), 4.42 (m, 1H), 4.91 (t, J = 6.5 Hz, 1H), 4.99 (t, J = 7.3 Hz, 1H), 5.14 (m, 4H), 5.33 (m, 2H), 5.51 (d, J = 8.1 Hz, 1H), 5.95 (d, J = 8.5 Hz, 1H), 7.29 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 20.7, 20.8, 23.1, 30.8, 35.2, 49.9, 53.4, 61.3, 66.8, 67.1, 67.6, 67.7, 69.7, 70.6, 70.7, 126.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 129.7, 135.2, 168.8, 169.5, 170.5, 170.6, 171.4. HRMS Calcd for $C_{35}H_{42}N_2O_{12}$ (M^+): 682.2738. Found: 682.2752. Compound **7e**: R_f = 0.30 (75% EtOAc/pet. ether) IR (film, NaCl) 3345, 3030, 2960, 1746, 1667, 1536, 1379, 1239, 1055, 767, 706 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.89 (s, 3H), 1.99 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 2.55 (m, 2H), 3.86 (m, 1H), 4.06 (m, 1H), 4.20 (dd, J = 5.0, 7.0 Hz,1H), 4.34 (m, 1H), 4.45 (m, 2H), 5.08 (m, 7H), 5.64 (m, 2H), 5.98 (m, 1H), 7.32 (m, 10H). ^{13}C NMR ($CDCl_3$) δ 20.5, 20.6, 22.8, 30.5, 35.7, 50.9, 53.7, 62.1, 66.9, 67.3, 68.5, 70.1, 70.7, 73.6, 127.9, 128.1, 128.2, 128.4, 128.5, 128.6,131.7, 134.9, 169.0, 169.1, 170.2, 170.6, 170.9, 171.1. HRMS Calcd for $C_{34}H_{40}N_2O_{12}$ (M^+): 668.2581. Found: 668.2606. Compound **B** (R^2 = Ac): R_f = 0.36 (35% EtOAc/pet. ether) IR (film, NaCl) 2960, 2917, 1754, 1449, 1379, 1238, 1047, 916, 732 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.74 (d, J = 6.5 Hz, 3H), 1.96 (s, 3H), 1.97 (s, 3H), 1.98 (s, 3H), 2.04 (s, 3H), 3.90 (m, 1H), 4.01 (dd, J = 2.3, 12.3 Hz, 1H), 4.18 (dd, J = 4.6, 12.3 Hz, 1H), 4.64 (m, 1H), 4.98 (m, 2H), 5.30 (t, J = 10.0 Hz, 1H), 5.66 (m, 1H), 5.86 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 18.8, 21.1, 21.2, 62.8, 69.5, 69.6, 71.1, 71.2, 73.6, 123.2, 134.7, 169.9, 170.1, 170.7, 171.2 HRMS Calcd for $C_{17}H_{24}O_9$ (M^+): 373.1420. Found: 373.1499. See also Ref. 2.

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