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Synthesis of α- and β-*C*-glycosides of *N*-acetylglucosamine

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Abstract—As part of efforts to make available new classes of bioactive *C*-glycoconjugates, D-glucosamine has been effectively converted into a series of 2-deoxy-2-amino-*C*-glycosides. This versatile approach is keyed by a remarkably effective metal catalyzed olefin isomerization of the isomeric *C*-allyl amino sugars which, in turn, are readily available via radical allylation of D-glucosamine.

Cell surface glycoconjugates provide an information rich matrix that mediates cellular interactions with other cells and with extracellular components. In this context, glycoproteins have been shown to be relevant in numerous important disease states.[1] The protein is typically conjugated to a carbohydrate moiety through a 2-deoxy-2-amino sugar, including both α- and β-linked glucosamine and galactosamine (examples in Figure 1). The carbohydrate epitopes of these conjugates have been shown to play a central role in a variety of significant biological events, including immune response, inflammation, metastasis, and bacterial and viral infection, among others.[2] There is considerable interest in developing effective therapeutic strategies based upon recognition of these cell surface carbohydrates.

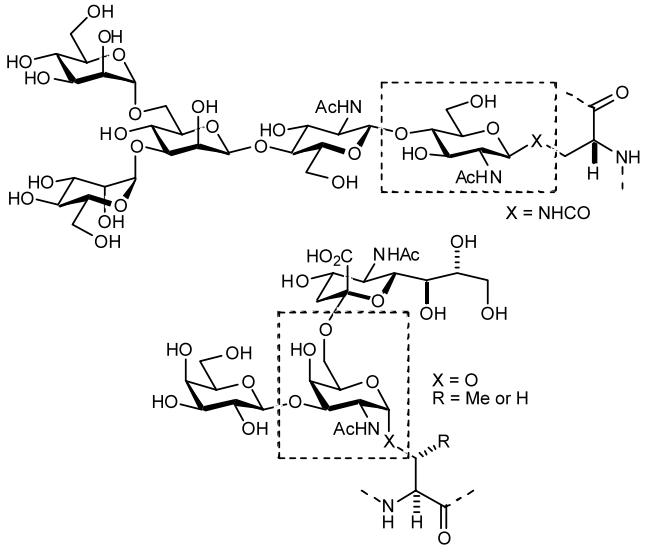

Figure 1. Representative glycopeptide structures.

Studies to understand the structural features of cellular communication and to develop stable carbohydrate-based therapeutic agents have been complicated by the intrinsic lability of the *N*- or *O*-acetal linkages between the carbohydrate and its bioconjugate. An intriguing approach to the solution of this problem lies in the replacement of the exocyclic heteroatom with a carbon to afford *C*-glycosidic analogues that are impervious to degradation by glycosidases (i.e. X = carbon linkage in Figure 1). This has focused considerable attention on the synthesis and properties of these unnatural analogues.[3]

Despite structural investigations that have revealed notable conformational differences between the natural and unnatural glycosides,[4] largely attributed to the *exo*-anomeric effect,[5] a number of studies comparing the natural *O*-glycosides with their *C*-glycoside analogues in biological settings have shown that the biological properties of the carbohydrates are retained.[6] Two recent reports are particularly relevant to the present studies. In one, a peptide fragment of type II collagen incorporating a *C*-glycoside analogue of β-D-galactosyl hydroxyvaline was evaluated for its immunogenicity versus helper T-cell hybridomas obtained from a mouse model for rheumatoid arthritis and was found to be active, albeit at higher concentrations than the corresponding natural *O*-glycopeptide.[7] In another study, an exact *C*-glycoside of a glucosamine glycerolipid was found to display virtually identical antiproliferative activity to the *O*-glycosidic analogue.[8]

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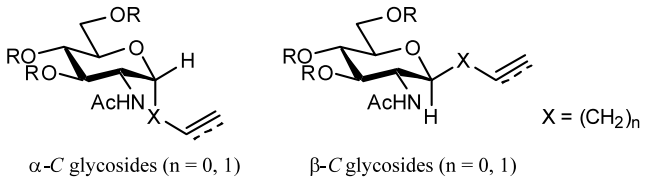
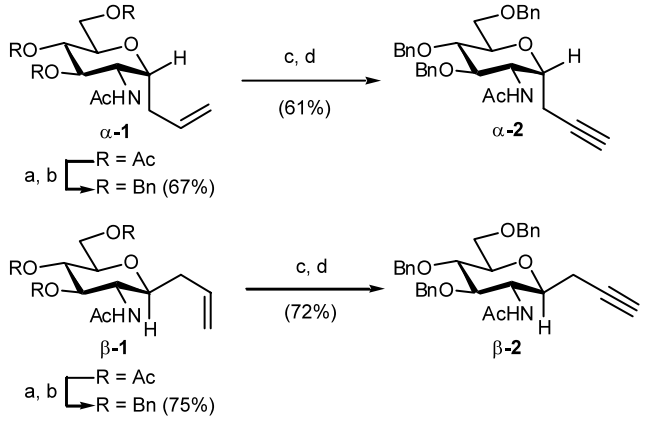


Figure 2.



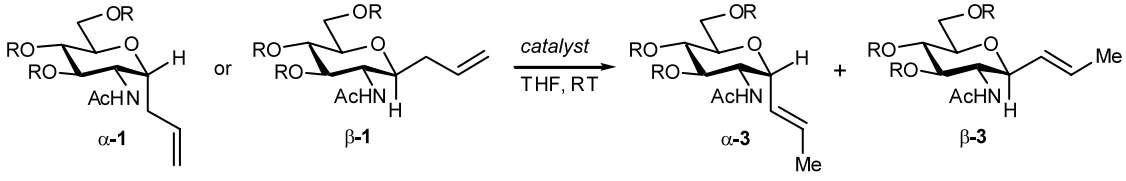
Scheme 1. *Reagents and conditions*: (a) NaOMe, MeOH. (b) BnBr, NaH, DMF, rt. (c) OsO_4, $NaIO_4$, THF/H_2O, rt. (d) $MeCOC(N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, rt.[28]

With such encouraging results as a backdrop, we have embarked on studies directed toward understanding and exploiting recognition events based upon cell surface glycoproteins using stable *C*-glycoside analogues.[9] Toward this objective, we sought to develop general accessibility to a range of stereoisomeric 2-deoxy-2-amino-*C*-glycosides that may be used to access *C*-glycopeptide structures related to the types shown in Figure 1. The preparation of *C*-glycosides of 2-amino sugars has proven difficult and, consequently, there are relatively few methods reported.[10,11] We initially focused our attention on the preparation of the olefinic and acetylenic derivatives of glucosamine shown in Figure 2 with the expectation that our results would translate to other 2-amino carbohydrate substrates.

Application of the radical allylation procedures reported by Horton[12] and Bertozzi[13] allowed the preparation of the α- and β-anomers of acetate protected *C*-allyl glucosamine (α-**1** and β-**1**, R = Ac, Scheme 1) in serviceable yields and quantities. Following a protecting group exchange (R = Ac→R = Bn), the desired propargyl glycosides, α-**2** and β-**2**, were efficiently obtained by routine oxidative double bond cleavage[14] followed by exposure to Ohira's reagent.[15] Though synthetically unremarkable, this route provides a suitable solution to the lack of direct propargylation methodology.[16]

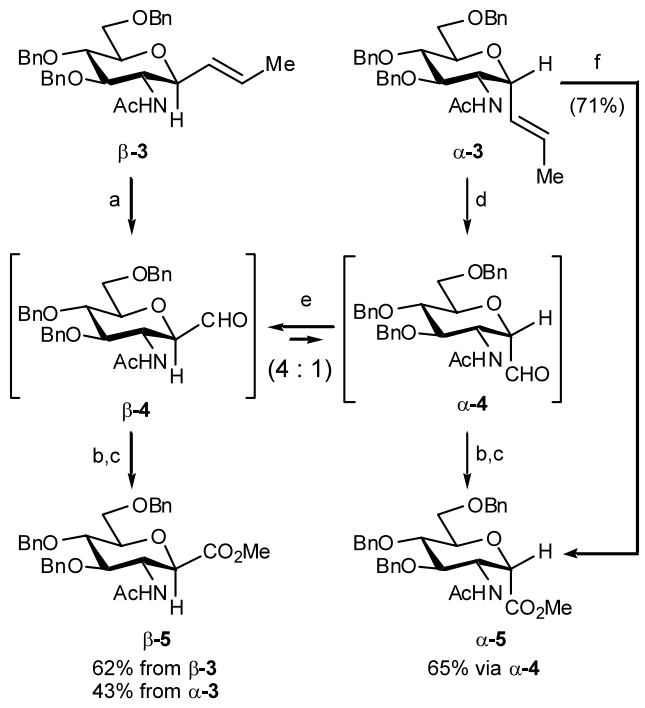
Toward expanding the repertoire of available *C*-glycosides, we examined metal-catalyzed isomerization of these allyl species. Following the report of Wong and co-workers,[17] the benzyl-protected α-isomer, α-**1**, was exposed to 40 mol% $PdCl_2$ in refluxing benzene for 24 h to afford a 65% yield of the pure disubstituted olefin α-**3** following careful column chromatography (entries 1, Table 1). In the course of efforts to improve the availability of this valuable intermediate, we observed that the isomerization could be effected more rapidly and under much milder conditions using the cationic iridium catalyst, $(PhMe_2P)_2IrCOD^+PF_6^-$ (entries 2, Table 1).[18] Further studies revealed that the yield of the desired isomer was significantly improved by decreasing the amount of catalyst (entries 3–5, Table 1). In addition, it was noted that extension of the reaction times had a deleterious effect on the yield of the product, perhaps as a consequence of over isomerization. Significantly, the isomerization of the analogous peracetylated substrate could be effected as well, though longer reaction times were required and some anomeric epimerization was noted (entries 6, Table 1). Guided by these results, we chose 10 mol% of the catalyst as the standard conditions to effect this isomerization. It was gratifying to find that these conditions could be successfully applied to the β-anomer as well to afford both benzyl and acetate protected vinyl glycosides β-**3**

Table 1.

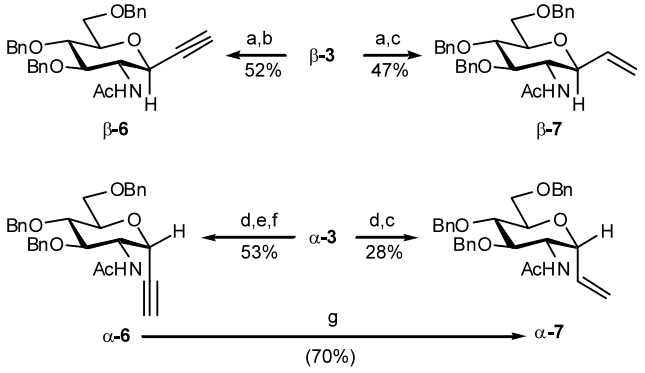


Entries	Substrate (R)	Catalyst	Mol%	Time (h)	α-**3**:β-**3**	Yield (%)
1[a]	α-**1** (Bn)	$PdCl_2$	40	24	100:0	65
2	α-**1** (Bn)	$(Ph_2Me)_2IrCOD{\cdot}PF_6$	40	2.5	100:0	65
3	α-**1** (Bn)	$(Ph_2Me)_2IrCOD{\cdot}PF_6$	20	2	100:0	67
4	α-**1** (Bn)	$(Ph_2Me)_2IrCOD{\cdot}PF_6$	10	2	100:0	87
5	α-**1** (Bn)	$(Ph_2Me)_2IrCOD{\cdot}PF_6$	5	2	100:0	86
6	α-**1** (Ac)	$(Ph_2Me)_2IrCOD{\cdot}PF_6$	10	20	10:1	92
7	β-**1** (Bn)	$(Ph_2Me)_2IrCOD{\cdot}PF_6$	10	2	0:100	60
8	β-**1 (Ac)**	**$(Ph_2Me)_2IrCOD{\cdot}PF_6$**	**10**	**20**	**1:6**	**80**

[a] Carried out in refluxing PhH.[28]



Scheme 2. *Reagents and conditions*: (a) OsO_4, $NaIO_4$, THF/H_2O, rt. (b) $NaClO_2$, $NaHPO_4$, 2-methyl-2-butene, THF/^iPrOH, rt. (c) $TMSCHN_2$, MeOH/PhH, rt. (d) O_3, CH_2Cl_2; Ph_3P. (e) K_2CO_3, CH_2Cl_2/MeOH (1α:4β). (f) O_3, MeOH, NaOH.[28]



Scheme 3. *Reagents and conditions*: (a) OsO_4, $NaIO_4$, THF/H_2O, rt. (b) $AcC(N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, rt. (c) $Ph_3P{=}CH_2$, THF, 0°C. (d) O_3, CH_2Cl_2; Ph_3P. (e) CBr_4, Ph_3P, CH_2Cl_2, rt. (f) LDA (4 equiv.), THF, −78°C. (g) H_2, Pd on $BaSO_4$, PhH.[28]

(entries 7 and 8, Table 1), albeit in somewhat lower yields and with more isomerization accompanying the formation of the acetate product.

With isomeric vinyl glycosides α-**3** and β-**3** in hand, access to additional *C*-glycosidic derivatives was explored. Oxidative cleavage of β-vinyl glycoside β-**3** using Lemieux conditions[14] cleanly afforded the unstable equatorial aldehyde β-**4** that, without purification, could be oxidized[19] and methylated[20] to yield the β-methyl ester β-**5** in good overall yield (Scheme 2). Likewise, oxidation of the α-**3** was examined under a

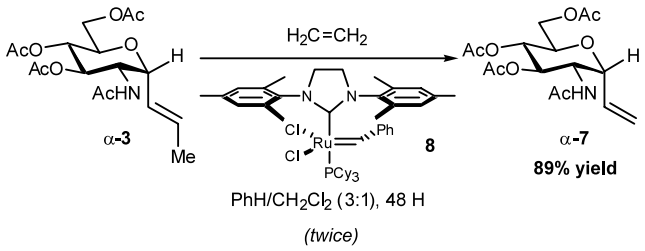


Figure 3.

variety of conditions including the Lemieux conditions, dihydroxylation ($K_2OsO_4{\cdot}H_2O$, $K_3Fe(CN)_6$)/oxidative cleavage ($Pb(OAc)_4$), and ozonolysis, with the latter giving the desired aldehyde α-**4** in >90% yield as judged by NMR analysis of the crude product.[21] This intermediate could be processed to the axial ester in a similar manner (65% overall). Analogous to a report by Bednarski and co-workers,[22] epimerization of this aldehyde to the β-isomer could be effected using mild base to afford a 4:1 mixture of anomers favoring β-**4**, thus offering synthetic entrée to both *C*-glycosides anomers from a single intermediate, α-**3**. An even more expeditious means to the α-methyl ester could be realized through ozonolysis using Marshall's protocol.[23]

Aldehydes α-**4** and β-**4** appeared to be attractive intermediates for the preparation of the targeted vinylic and acetylenic *C*-glycosides (see Figure 2). The configurationally stable β-anomer could be straightforwardly transformed into the corresponding alkynyl β-**6**[15] and vinyl derivatives β-**7** using standard methodology, albeit in modest overall yields from β-**3** (Scheme 3). However, the configurational lability of the α-aldehyde proved problematic and prompted a broader investigation. Treatment of aldehyde α-**4** with the Ohira reagent[15] led to significant isomerization (53% of a 1:1 mixture of α:β acetylenes) and the application of the $TMSCHN_2$ methodology[24] led to unacceptably poor yields (15%). Fortunately, the Corey–Fuchs protocol led to the desired alkyne α-**6** in acceptable overall yield from olefin α-**3** as a single isomer.[25] Olefination of aldehyde α-**4** to provide vinyl derivative α-**7** also proved troublesome being plagued by epimerization and low yields. As indicated, standard Wittig olefination gave the olefin in poor yield, as did a variety of titanium-mediated olefinations.[26] A modest improvement in the overall yield to this vinyl compound could be realized through semi-reduction of the acetylene α-**6**.

The configurational lability of the α-aldehyde prompted a more detailed study of the methods by which the vinyl *C*-glycosides could be accessed. An effective solution is illustrated in Figure 3, wherein olefin metathesis of the propenyl glycoside α-**3** with ethylene using 20 mol% of Grubb's second generation catalyst **8** afforded the target vinyl glycoside α-**7** in high yield with no discernible loss of stereochemistry.[27] At the end of 48 h, this metathesis had proceeded to about 90% completion, thus requiring a second exposure to the metathesis conditions to effect complete conversion. In this manner, the acetate protected vinyl glycoside becomes avail-

able in 82% overall yield in two steps from the allyl glycoside α-**1**. Attempts to expand this approach to the β-isomer, β-**3**, were not met with similar success as ethylene metathesis proceeded to only ~70% conversion under the same conditions.

In summary, we have demonstrated synthetic accessibility to a variety of glucosamine *C*-glycosides that promise to prove useful in the preparation of novel *C*-glycoconjugates. It is further anticipated that the present methods will be readily extended to other 2-deoxy-2-amino carbohydrates to allow a wide range of functionalized *C*-glycosides to be obtained. Of particular note is the efficient metal catalyzed isomerization of readily available allyl *C*-glycosides to afford propenyl *C*-glycosides α- and β-**3** which represent stable intermediates that are anticipated to be valuable building blocks for the preparation of complex, biologically important oligosaccharides. The application of these intermediates to the preparation of *C*-glycopeptides will be reported in due course.

Acknowledgements

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27. For a recent example of ethylene metathesis, see: Pietraszuk, C.; Marciniec, B.; Jankowska, M. *Adv. Synth. Catal.* **2002**, *344*, 789–793.
28. Selected spectral data: α-**2**: ^1H NMR ($CDCl_3$) δ 1.83 (s, 3H), 1.98 (t, $J=2.2$ Hz, 1H), 2.36 (dd, $J=6.8$, 2.6 Hz, 2H), 3.58 (t, $J=1.3$ Hz, 1H), 3.80 (m, 3H), 4.10 (dt, $J=5.2$, 1.3 Hz, 1H), 4.46 (m, 6H), 6.53 (d, $J=9.8$ Hz, 1H), 7.29 (m, 15H); ^{13}C NMR ($CDCl_3$) δ 21.7, 23.2, 46.9, 66.9, 67.5, 69.8, 71.7, 72.0, 72.9, 73.3, 74.1, 75.4, 80.4, 127.5, 127.6, 127.7, 127.9, 128.0, 128.3, 128.4, 128.5, 137.2, 138.1, 169.9. β-**2**: ^1H NMR ($CDCl_3$) δ 1.80 (s, 3H), 1.97 (t, $J=5.4$ Hz, 1H), 2.48 (m, 2H), 3.67 (m, 7H), 4.61

(m, 5H), 4.83 (dd, $J=17.5$, 11.6 Hz, 1H), 5.12 (d, $J=7.6$ Hz, 1H), 7.27 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 22.8, 23.5, 55.3, 68.8, 69.7, 73.4, 74.5, 74.8, 76.7, 78.9, 79.3, 80.8, 82.3, 127.5, 127.81, 127.89, 127.9, 128.1, 128.3, 128.4, 128.5, 137.9, 138.2, 138.3, 170.3. α-**3** (R = Bn): ^{1}H NMR ($CDCl_3$) δ 1.18 (d, $J=6.3$ Hz, 3H), 1.82 (s, 3H), 3.73 (m, 4H), 4.24 (m, 2H), 4.41 (d, $J=5.7$ Hz, 1H), 4.56 (m, 6H), 5.42 (ddd, $J=10.5$, 4.8, 1.5 Hz, 1H), 5.76 (m, 1H), 6.19 (d, $J=9.2$ Hz, 1H), 7.29 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 18.0, 23.3, 48.7, 67.8, 69.4, 72.2, 72.4, 73.2, 73.9, 74.7, 75.1, 126.7, 127.63, 127.67, 127.7, 127.8, 127.9, 128.3, 128.4, 130.0, 137.5, 137.7, 138.1, 169.6. α-**3** (R = Ac): ^{1}H NMR ($CDCl_3$) δ 1.74 (d, $J=6.5$ Hz, 3H), 1.87 (s, 3H), 1.99 (s, 3H), 2.03 (s, 3H), 3.87 (m, 1H), 4.02 (dd, $J=2.7$, 9.0 Hz, 1H), 4.17 (dd, $J=5.0$, 6.9 Hz, 1H), 4.28 (m, 1H), 4.49 (t, $J=6.6$ Hz, 1H), 5.01 (m, 2H), 5.74 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 18.2, 20.4, 20.5, 20.6, 23.0, 51.2, 62.2, 68.5, 69.7, 71.0, 74.1, 122.5, 134.9, 169.1, 169.8, 170.6, 171.5. β-**3** (R = Bn): ^{1}H NMR ($CDCl_3$) δ 1.66 (dd, $J=6.3$, 1.3 Hz, 3H), 1.78 (s, 3H), 3.48 (m, 1H), 3.67 (m, 6H), 4.61 (m, 4H), 4.82 (dd, $J=16.2$, 11.3 Hz, 2H), 4.97 (d, $J=6.1$ Hz, 1H), 5.47 (dd, $J=15.3$, 5.7 Hz, 1H), 5.70 (m, 1H), 7.17 (m, 2H), 7.31 (m, 13H). ^{13}C NMR ($CDCl_3$) δ 17.8, 23.4, 55.2, 68.9, 73.4, 74.4, 74.8, 78.7, 80.1, 82.8, 127.5, 127.7, 127.8, 127.9, 128.1, 128.3, 128.4, 130.9, 138.03, 138.08, 138.4, 169.7. β-**3** (R = Ac): ^{1}H NMR ($CDCl_3$) δ 1.67 (d, $J=6.6$ Hz, 3H), 1.87 (s, 3H), 1.99 (s, 3H), 2.00 (s, 3H), 2.06 (s, 3H), 3.67 (m, 2H), 4.05 (m, 2H), 4.20 (dd, $J=4.6$, 12.0 Hz, 1H), 5.05 (m, 2H), 5.46 (dd, $J=7.6$, 15.4 Hz, 1H), 5.59 (d, $J=9.2$ Hz, 1H), 5.74 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.4, 21.0, 21.1, 21.2, 23.7, 54.0, 62.9, 69.0, 74.7, 76.1, 81.3, 123.0, 132.7, 169.8, 170.4, 171.3, 171.9. α-**5**: ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3H), 3.65 (t, $J=8.7$ Hz, 1H), 3.74 (m, 6H), 4.14 (m, 1H), 4.58 (m, 8H), 6.40 (d, $J=8.7$ Hz, 1H), 7.28 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 23.2, 47.9, 52.2, 67.3, 69.9, 72.6, 72.9, 73.2, 74.1, 75.4, 75.6, 127.6, 127.7, 127.94, 127.96, 128.3, 137.8, 169.6, 170.3. β-**5**: ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3H), 3.54 (m, 1H), 3.73 (m, 7H), 3.96 (m, 2H), 4.61 (m, 4H), 4.83 (dd, $J=16.5$, 11.9 Hz, 1H), 5.17 (d, $J=6.3$ Hz, 1H), 7.26 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 23.2, 52.5, 53.3, 68.6, 73.4, 74.5, 74.9, 77.5, 78.3, 79.2, 81.4, 127.6, 127.9, 128.0, 128.31, 128.36, 128.44, 128.60, 128.69, 137.9, 138.1, 168.8, 170.2. α-**6**: ^{1}H NMR ($CDCl_3$) δ 1.76 (s, 3H), 2.48 (d, $J=2.4$ Hz, 1H), 3.73 (m, 4H), 3.96 (m, 1H), 4.17 (m, 1H), 4.58 (m, 4H), 4.83 (m, 3H), 4.97 (d, $J=8.3$ Hz, 1H), 7.29 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 18.8, 23.3, 48.7, 67.8, 69.4, 72.2, 72.4, 73.2, 73.9, 74.7, 75.1, 126.7, 127.63, 127.67, 127.7, 127.8, 127.9, 128.3, 128.4, 130.0, 137.5, 137.7, 138.1, 169.6. β-**6**: ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H), 2.43 (d, $J=1.9$ Hz, 1H), 3.50 (m, 1H), 3.71 (m, 4H), 3.91 (t, $J=9.8$ Hz, 1H), 4.39 (dd, $J=10.1$, 1.7 Hz, 1H), 4.60 (m, 4H), 4.82 (dd, $J=17.1$, 11.6 Hz, 1H), 5.51 (d, $J=8.3$ Hz, 1H), 7.24 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 23.1, 56.0, 68.2, 68.3, 73.1, 74.0, 74.4, 74.5, 78.1, 78.9, 79.3, 81.2, 127.2, 127.5, 127.7, 128.01, 128.06, 128.1, 137.5, 137.9, 170.0. α-**7** (benzyl protected): ^{1}H NMR ($CDCl_3$) δ 1.82 (s, 3H), 3.61 (t, $J=2.6$ Hz, 1H), 3.79 (m, 3H), 4.27 (m, 2H), 4.57 (m, 7H), 5.29 (ddt, $J=29.0$, 17.3, 1.5 Hz, 1H), 5.77 (ddd, $J=17.2$, 10.7, 4.8 Hz, 1H), 6.31 (d, $J=9.4$ Hz, 1H), 7.30 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 23.2, 48.2, 67.6, 72.0, 72.1, 72.2, 73.1, 73.2, 73.5, 117.2, 127.6, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 132.3, 137.3, 137.5, 138.0, 169.7. α-**7** (acetate protected) ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.06 (s, 3H), 3.95 (m, 1H), 4.07 (dd, $J=3.1$, 12.3 Hz, 1H), 4.22 (dd, $J=5.4$, 11.9 Hz, 1H), 4.33 (m, 1H), 4.62 (t, $J=5.8$ Hz, 1H), 5.02 (m, 2H), 5.43 (m, 2H), 5.84 (d, $J=8.5$ Hz, 1H), 5.98 (ddd, $J=4.2$, 6.2, 10.8, 1H); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.5, 20.6, 20.7, 23.0, 51.2, 62.1, 68.4, 70.2, 73.8, 121.9, 130.0, 169.1, 169.8, 170.6, 171.5. β-**7**: ^{1}H NMR ($CDCl_3$) δ 1.78 (s, 3H), 3.50 (m, 1H), 3.74 (m, 6H), 4.60 (m, 4H), 4.84 (dd, $J=15.3$, 11.6 Hz, 2H), 5.03 (m, 1H), 5.24 (m, 2H), 5.83 (m, 1H), 7.27 (m, 15H). ^{13}C NMR ($CDCl_3$) δ 23.5, 55.0, 68.9, 73.5, 74.4, 74.8, 78.7, 78.9, 80.2, 82.6, 118.7, 127.6, 127.8, 128.0, 128.1, 128.3, 128.4, 128.5, 135.0, 138.0, 138.4, 169.9.