Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 2449–2453

TETRAHEDRON LETTERS

Short, stereoselective synthesis of *C*-glycosyl asparagines via an olefin cross-metathesis

Ernest G. Nolen,* Adam J. Kurish, Kelli A. Wong and Michael D. Orlando

Department of Chemistry, Colgate University, Hamilton, NY 13346, USA

Received 23 December 2002; revised 3 February 2003; accepted 6 February 2003

Abstract—The Grubbs second generation ruthenium catalyst was employed for the cross metathesis between α- and β-*C*-allyl glycosides and suitably protected L-vinyl glycines to furnish olefinic products in 57–94% yields. Hydrogenation afforded the *C*-glycosyl asparagines in high yield.

The importance of intercellular recognition based on *O*- and *N*-glycopeptides has led to their evaluation in biosynthetic studies and as pharmaceutical targets.[1] Numerous reports have described molecular mimics of these compounds by altering the nature of the connecting chain between the glycoside and the peptide or by appending saccharide groups on extended chains, often for the purpose of clustering groups of carbohydrates.[2] Others have sought to maintain an isosteric glycopeptide relationship by substituting a methylene for oxygen in the case of *C*-glycosyl serines and an ethylene for the amide functionality of glycosyl asparagines (Fig. 1). These isosteres serve as stable mimics and are expected to act as enzyme inhibitors. Versatile and simple methods for constructing the carbon-linked isosteres are highly desirable.

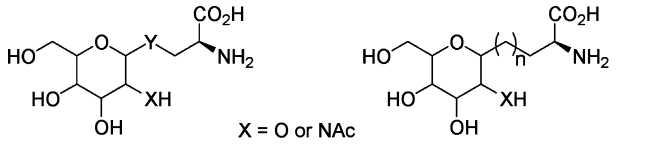


Figure 1. Isosteric mimics of *O*-glycosyl serine and *N*-glycosyl asparagine.

Previous synthetic work has explored a wide variety of C–C bond forming reactions for the preparation of *C*-glycosyl amino acids, and has been reviewed by Dondoni.[3] Since that review there have been several reports furthering the development of concise and broadly applicable routes to *C*-glycosyl amino acids utilizing the Ramberg–Bäcklund rearrangement,[4] acetylide couplings,[5] homochiral enolate additions,[6] and an asymmetric Strecker reaction.[7] The availability of the second generation Grubbs catalyst[8] has prompted the application of its use for elaboration of the *O*-glycosyl amino acids[9] and for the construction of *C*-glycosides.[10] Recently the ruthenium-catalyzed olefin cross-metathesis has been employed for the preparation of *C*-glycosyl amino acids. Dondoni made use of benzyl-protected *C*-alkenyl glycosides and affected cross-metathesis with a vinyl oxazolidine, derived from Garner's aldehyde, yielding products with 2–4 carbons linking the anomeric position to the glycinyl moiety.[11] McGarvey recently described the success of the cross-metathesis approach between *C*-alkenyl glycosides and L-allyl glycine to yield a 3 or 4 carbon linkage.[12] These reports have encouraged us to communicate our approach based on the olefin cross-metathesis between *C*-allyl glycosides and L-vinyl glycines. Our metathesis alkene products, with 2 or 3 linking methylenes, can in some cases be hydrogenated to yield substrates directly suited for solid-phase peptide synthesis.

Our synthetic approach begins with the important stereochemical elements at the anomeric position and the glycinyl α-carbon intact. The α- and β-*C*-allyl glycosides have been widely utilized, including the α-*C*-allyl GlcNAc.[13] The *C*-vinyl glycosides were salvaged from iodide eliminations in our previous work.[6] The

Keywords: cross-metathesis; *C*-glycosyl amino acid; *C*-glycosyl asparagine; vinyl glycines; *C*-allyl glycoside.

* Corresponding author. Tel.: 315-228-7234; fax: 315-228-7935; e-mail: enolen@mail.colgate.edu

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00350-2

N-Cbz L-vinyl glycine methyl ester **2** was readily available by periodate oxidation of methionine and thermal elimination using the protocol of Rapoport.[14] Upon sulfoxide elimination, compound **2** distills out of the reaction mixture. During the distillation it is imperative that temperatures do not exceed 150°C, otherwise alkene isomerization to the α,β-unsaturated ester interferes. This oxidation/elimination sequence produces multigram quantities in 40% overall yield from methionine methyl ester, and provides an inexpensive substrate for our cross-metathesis studies. Attempts to apply the same method to *N*-Boc vinyl glycine benzyl ester **3** failed due to alkene isomerization at the temperatures necessary for sulfoxide elimination. The known *N*-Boc vinyl glycine[15] and the *N*-Fmoc vinyl glycine benzyl ester **4** were prepared by lead tetraacetate elimination of suitably protected L-glutamic acid derivatives following the procedure of Hanessian.[16] As in earlier reports the products of this decarboxylative elimination unfortunately required chromatography to separate recovered starting material and some γ-methyl ester.[16]

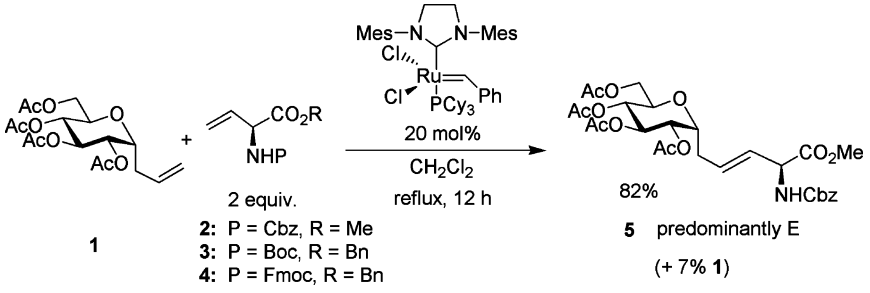
Cross-metathesis is achieved in high yields for the *C*-allyl glycosides using Grubbs' second generation catalyst, as shown in Scheme 1 by the cross-metathesis of the α-isomer of tetra-*O*-acetylglucose with the *N*-Cbz vinyl glycine methyl ester. Table 1 presents our results from the cross-metathesis and hydrogenation reactions.[17] All cross-metatheses were initially conducted with 20 mol% of the 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene ruthenium complex by refluxing in dichloromethane for 12 h with 2 equiv. of the vinyl glycine. In all cases, the mass balance for the reaction was well accounted for by recovered starting *C*-allyl glycosides, traces of benzylidene cross-metathesis products, and self-metathesis of the vinyl glycine component. We also found that equally good results were obtained using 10 mol% Ru-catalyst allowing for a slightly extended time (16 h); however, the reaction times were not optimized. Attempts to significantly shorten the reaction time by increasing the reflux temperature using either carbon tetrachloride or 1,2-dichloroethane led to significantly lower yields in agreement with Dondoni's report.[11] At elevated temperatures double bond isomerizations were noted for the *C*-allyl glycosides[18] and for the vinyl glycine, which appear to inhibit further reaction.

No significant differences are apparent between the reactions with acetate versus benzyl protected *C*-allyl glycosides (Table 1, entries 1 and 2). Likewise the *N*-Cbz, *N*-Boc, and *N*-Fmoc (entries 6–8), all display similar reactivity, which is significant in view of several reports emphasizing the effects associated with proximal functional groups on catalytic ruthenium-based metatheses.[19] While most reactions were high yielding, the *C*-vinyl glycosides proved not to be good cross-metathesis partners. Yields ranging from 11–32% were obtained with high percentages of recovered starting materials. This is comparable with the study by Dondoni,[11] and necessitates further exploration to produce *C*-glycosyl serine mimics, although McGarvey does observe cross-metathesis participation with *C*-(1-propenyl) glycosides.[12] Unfortunately, these *C*-(1-propenyl) glycosides are unreactive with vinyl glycine **2** under typical cross metathesis conditions.

As an alternative approach to shorten the chain between the anomeric carbon and the glycinyl group, we sought to prepare a trisubstituted olefin by cross-metathesis.[20] Preparation of alkene **6**, previously described by Toone,[21] was attempted (Scheme 2), via cross-metathesis of the *C*-allyl glycoside **1** with a dehydroalanine derivative **7**,[22] but only self-metathesis of the *C*-allyl glycoside was observed.

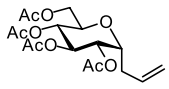
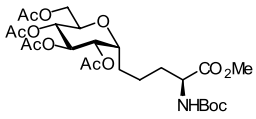
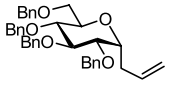
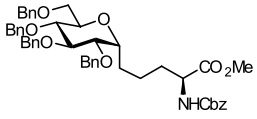
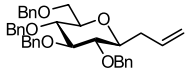
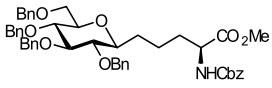
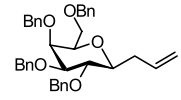
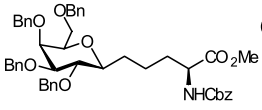
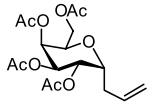
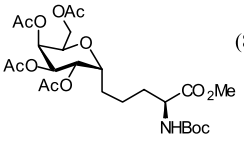
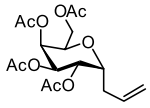
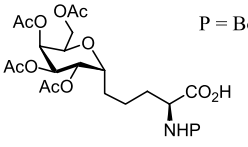
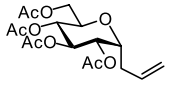
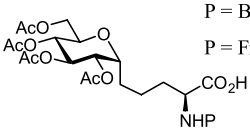
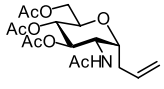
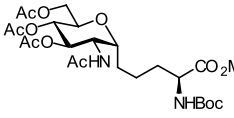
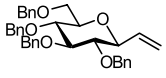
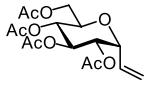
The cross-metathesis products have been hydrogenated to afford the protected *C*-glycosyl asparagines. Sole reduction of the alkene has been achieved by hydrogenation using Pt on alumina (entries 2–4). Reduction of the alkene with concomitant Boc-protection[23] proceeded cleanly via Pd/C catalysis (entries 1, 5, and 10). Finally, to provide carboxylic acids for solid-phase peptide synthesis, hydrogenation of the alkene along with hydrogenolysis of the benzyl ester using Pd/C afforded the *C*-glycosyl asparagines (entries 6–9).

In conclusion, this letter presents a short synthesis of stable α- and β-glycosyl asparagine mimics from inexpensive, readily available precursors by way of two catalytic reactions: a ruthenium-based olefin cross-metathesis followed by palladium or platinum hydrogenation.



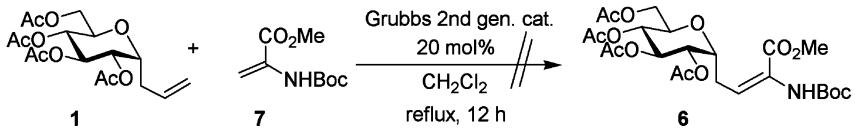
Scheme 1. Example olefin cross-metathesis.

Table 1. Percent yield of cross-metathesis (CM) products and products from hydrogenation reactions

Entry	*C*-Alkenyl glycosides	Vinyl glycines	CM % yield[a] (rec'd SM %)	Hydrogenation products (%yield)
1		**2**	82 (7)	 (90)[b]
2		**2**	64 (24)	 (85)[c]
3		**2**	82	 (90)[c]
4		**2**	74 (14)	 (92)[c]
5		**2**	62	 (80)[b]
6		**3**	86	 P = Boc (89)[b]
7		**4**	72	---
8		**3**	94	P = Boc (99)[d]
9		**4**	77	 P = Fmoc (90)[d]
10		**2**	57	 (54)[b]
11		**2**	32 (56)	---
12		**2**	11 (79)	---

[a]The reaction was refluxed for 12 h in dichloromethane with 20 mol% Ru-catalyst and 2 equivalents of the vinyl glycine.

[b]Hydrogenation with Pd/C and Boc-anhydride. [c]Hydrogenation with Pt on alumina. [d]Hydrogenation with Pd/C



Scheme 2. Unsuccessful cross-metathesis leading to trisubstituted olefin.

Acknowledgements

Partial support of this work was provided by the National Science Foundation's CCLI Program (DUE-0088227). Undergraduates, A.J.K. and M.D.O., thank Merck/AAAS for summer support, and appreciation is extended to A. Attygalle of the Stevens Institute of Technology for mass spectral data.

References

1. (a) *Glycoproteins and Human Disease*; Brockhausen, I.; Kuhns, W., Ed.; Chapman and Hall: New York, 1997; (b) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357–2364; (c) Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science* **2001**, *291*, 2370–2376.
2. (a) Allen, J. R.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 10875–10882; (b) Nagy, J. O.; Wang, P.; Gilbert, J. H.; Schaefer, M. E.; Hill, T. G.; Callstrom, M. R.; Bednarski, M. D. *J. Med. Chem.* **1992**, *35*, 4501–4502; (c) Lundquist, J. J.; Toone, E. J. *Chem. Rev.* **2002**, *102*, 555–578.
3. Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395–4422.
4. Paterson, D. E.; Griffin, F. K.; Alcaraz, M.-L.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2002**, 1323–1336.
5. (a) Dondoni, A.; Mariotti, G.; Marra, A. *J. Org. Chem.* **2002**, *67*, 4475–4486; (b) Dondoni, A.; Mariotti, G.; Marra, A.; Massi, A. *Synthesis* **2001**, 2129–2137.
6. Nolen, E. G.; Watts, M. M.; Fowler, D. J. *Org. Lett.* **2002**, *4*, 3963–3965.
7. Vincent, S. P.; Schleyer, A.; Wong, C.-H. *J. Org. Chem.* **2000**, *65*, 4440–4443.
8. Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953–956.
9. (a) Biswas, K.; Coltart, D. M.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 6107–6110; (b) Dominique, R.; Das, S. K.; Roy, R. *Chem. Commun.* **1998**, 2437–2438; (c) Dominique, R.; Liu, B.; Das, S. K.; Roy, R. *Synthesis* **2000**, 862–868; (d) Dominique, R.; Roy, R. *Tetrahedron Lett.* **2002**, *43*, 395–398.
10. (a) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58–71; (b) See Ref. 9d; (c) Postema, M. H. D.; Piper, J. L. *Tetrahedron Lett.* **2002**, *43*, 7095–7099.
11. Dondoni, A.; Giovannini, P. P.; Marra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2380–2388.
12. McGarvey, G. J.; Benedum, T. E.; Schmidtmann, F. W. *Org. Lett.* **2002**, *4*, 3591–3594.
13. Roe, B. A.; Boojamra, C. G.; Griggs, J. L.; Bertozzi, C. R. *J. Org. Chem.* **1996**, *61*, 6442–6445.
14. Afzali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817–4820.
15. Tashiro, T.; Fushiya, S.; Nozoe, S. *Chem. Pharm. Bull.* **1988**, *36*, 893–901.
16. Hanessian, S.; Sahoo, S. P. *Tetrahedron Lett.* **1984**, *25*, 1425–1428.
17. Products were successfully characterized by ^{1}H, ^{13}C, and 2D NMR spectroscopy and by high resolution electrospray mass spectrometry. Selected data for the CM products from entries 2, 6, 9, and 10 in Table 1.
Entry 2. ^{1}H NMR: δ 5.95 (dt, $J=15.6$, 7.0 Hz, *H*-4), 5.59 (dd, $J=15.6$, 6.1 Hz, *H*-3), 5.43 (bd, $J=6.2$ Hz, N*H*), 5.15 (bs, CH_2 of Cbz), 4.98–4.84 (4×d, 5H, including *H*-2), 4.70–4.57 (4×d, 4H), 3.80–3.71 (m, 3H), 3.73 (s, OCH_3), 3.66 (t, $J=9.4$ Hz, 1H), 3.44 (bd, $J=9.4$ Hz, 1H), 3.33 (m, 2H), 2.62 (bd, $J=14.5$, 6.3 Hz, *H*-5a), 2.33 (m, *H*-5b); ^{13}C NMR: δ 87.7 (*C*-8), 81.8 (*C*-9), 79.4 (*C*H), 79.0 (*C*H), 78.7 (*C*H), 76.0, 75.5, 75.4, 73.8 (4×CH_2 of Bn), 69.3 (*C*-11), 67.5 (CH_2 of Cbz), 56.1 (*C*-2), 53.0 (OCH_3), 34.7 (*C*-5). Anal. calcd for $C_{48}H_{51}NO_9$: C, 73.36; H, 6.45; N, 1.78. Found: C, 73.03; H, 6.68; N, 1.79%.
Entry 6. ^{1}H NMR: δ 5.68 (m, *H*-3 and *H*-4), 5.39 (bs, *H*-9), 5.30 (bd, $J=6.0$ Hz, N*H*), 5.26–5.19 (m, *H*-7 and *H*-8), 5.18 (s, PhCH_2), 4.85 (bm, *H*-2), 4.25 (m, *H*-6 and *H*-10), 4.02 (m, *H*-11a,b), 2.45 and 2.25 (2×m, *H*-5a,b), 1.43 (s, *t*Bu); ^{13}C NMR: δ 155.4 (*C*=O of Boc), 80.4 (*C*Me$_3$), 71.3 (*C*-6), 69.0 (*C*-10), 68.7 (*C*H), 68.2 (*C*H), 67.7 (*C*H), 67.6 (Ph*C*H$_2$), 61.3 (*C*-11), 55.6 (*C*-2), 30.0 (*C*-5), 28.7 (C*Me*$_3$). Anal. calcd for $C_{31}H_{41}NO_{13}$: C, 58.57; H, 6.50; N, 2.20. Found: C, 59.18; H, 7.00; N, 1.97.
Entry 9. ^{1}H NMR: δ 5.72 (m, *H*-3 and *H*-4), 5.58 (bd, $J=7.7$ Hz, N*H*), 5.31 (t, $J=8.9$ Hz, *H*-8), 5.22 (s, PhCH_2), 5.09 (dd, $J=9.1$, 5.5 Hz, *H*-7), 5.00 (t, $J=8.9$ Hz, *H*-9), 4.92 (m, *H*-2), 4.48–4.35 (m, 2H), 4.32–4.17 (m, 3H), 3.96 (dd, $J=12.2$, 2.8 Hz, *H*-11a), 3.80 (ddd, $J=8.9$, 5.4, 2.8 Hz, *H*-10), 2.59 (m, *H*-5a), 2.36 (m, *H*-5b); ^{13}C NMR: δ 155.9 (C=O of Fmoc), 144.1, 141.7 (2×*C* of Fmoc), 125.5 and 120.4 (*C*-3 and *C*-4), 72.0 (*C*-6), 70.5 (*C*H), 70.4 (*C*H), 69.4 (*C*H), 69.1 (*C*H), 67.9 (CH_2), 67.5 (CH_2), 62.4 (*C*-11), 56.0 (*C*-2), 47.5 (*C*H of Fmoc), 29.4 (*C*-5). HRMS (ESI) calcd for MH^+ $C_{41}H_{44}NO_{13}$: 758.2813. Found: 758.2752.
Entry 10. ^{1}H NMR: δ 5.85 (d, $J=8.7$ Hz, *H*NAc), 5.05 (N*H* of Boc), 5.04 (t, $J=8.1$ Hz, *H*-8), 4.97 (t, $J=7.2$ Hz, *H*-9), 4.36 (dd, $J=12.1$, 6.5 Hz, *H*-11a), 4.29 (m, *H*-2), 4.26 (dt, $J=8.5$, 4.6 Hz, *H*-7), 4.11 (m, *H*-6 and *H*-11b), 3.86 (m, *H*-10), 3.76 (s, OCH_3), 2.13, 2.11, 2.09 (3×s, OAc CH_3), 1.46 (s, *t*Bu); ^{13}C NMR: δ 170.1 (*C*O$_2$Me), 71.9 (*C*H), 70.5 (2×*C*H), 68.3 (*C*-9), 62.1 (*C*-11), 53.4 (*C*-2), 52.7 (O*C*H$_3$), 32.8 (CH_2), 28.7

(CMe_3), 23.6, 21.5 (*C*-4). MS (ESI) 561.3 (M+H), 578.7 ($M+NH_4$) *m*/*z*.

18. Cadot, C.; Dalko, P. I.; Cossy, J. *Tetrahedron Lett*. **2002**, *43*, 1839–1841.
19. (a) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett*. **2002**, *43*, 2263–2267; (b) Basu, K.; Cabral, J. A.; Paquette, L. A. *Tetrahedron Lett*. **2002**, *43*, 5453–5456.
20. Chatterjee, A. K.; Grubbs, R. H. *Org. Lett*. **1999**, *1*, 1751–1753.
21. Debenham, S. D.; Debenham, J. S.; Burk, M. J.; Toone, E. J. *J. Am. Chem. Soc*. **1997**, *119*, 9897–9898.
22. Zhu, Y.-F.; Yamazaki, T.; Tsang, J. W.; Lok, S.; Goodman, M. *J. Org. Chem*. **1992**, *57*, 1074–1081.
23. Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett*. **1988**, *29*, 2983–2984.