ORGANIC LETTERS

2003
Vol. 5, No. 18
3269−3272

General Access to Iminosugar *C*-Glycoside Building Blocks by Means of Cross-Metathesis: A Gateway to Glycoconjugate Mimetics

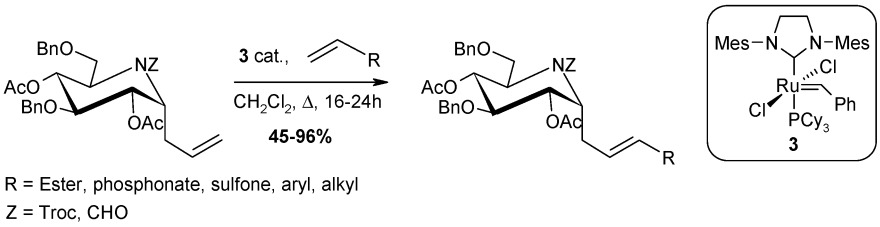
Guillaume Godin, Philippe Compain,* and Olivier R. Martin*

Institut de Chimie Organique et Analytique, UMR-CNRS 6005, Université d'Orléans, rue de Chartres, BP 6759, 45067 Orléans Cedex 2, France

philippe.compain@univ-orleans.fr; olivier.martin@univ-orleans.fr

Received June 18, 2003

ABSTRACT



R = Ester, phosphonate, sulfone, aryl, alkyl
Z = Troc, CHO

Cross-metathesis reactions of α-1-*C*-allyl-1-deoxynojirimycin derivatives 7a,b and various functionalized alkenes mediated by Grubbs's catalyst 3 are reported. The reactions showed reasonable to very good yields and excellent *E/Z* selectivity. This methodology allows the efficient and convergent synthesis of iminosugar *C*-glycosides with a great degree of structural diversity in the aglycone, opening the way to a variety of new glycoconjugate mimetics of biological interest.

Iminosugars form probably the most fascinating class of carbohydrate mimetics reported so far. Historically, they are best known for their role as powerful glycosidase inhibitors,[1] but more recently, the scope of their biological activities has been extended to the inhibition of various carbohydrate-processing enzymes such as glycosyltransferases[2] and nucleoside phosphorylases.[3] Since these enzymes are involved in a number of fundamental biological processes, iminosugars have recently entered the clinical field for assessment of their therapeutic potential in a wide range of diseases,[4] including viral infection, tumor metastasis, and lysosomal storage disorders. First successes are being recorded: *N*-butyl-1-deoxynojirimycin has recently been approved by the EMEA (European Agency for the Evaluation of Medicinal Products) for the treatment of type 1 Gaucher disease, a severe lysosomal disorder.[5] New exciting applications are being uncovered. For example, *N*-alkyliminosugars have been found to reversibly induce infertility in male mice, opening the way to a nonhormonal approach to male contraception.[6]

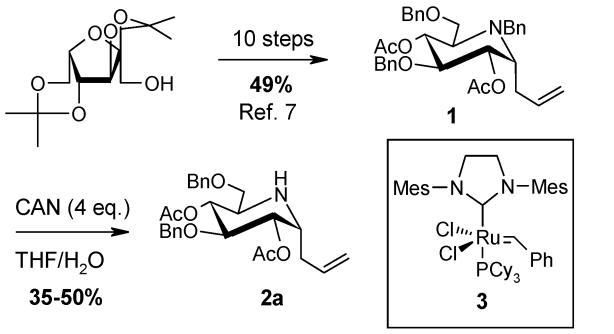
Considering the high potential of "azasugars" for drug discovery, general and efficient approaches to stable derivatives such as iminosugars *C*-glycosides are still needed to facilitate the exploration of new biological targets and the

(1) Stütz, A. E. *Iminosugars as Glycosidase Inhibitors: Nojirimycin and Beyond*; Wiley-VCH: Weinheim, 1999.
(2) (a) Compain, P.; Martin, O. R. *Bioorg. Med. Chem.* **2001**, *9*, 3077. (b) Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541. (c) Sears, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300.
(3) (a) Fedorov, A.; Shi, W.; Kicska, G.; Fedorov, E.; Tyler, P. C.; Furneaux, R. H.; Hanson, J. C.; Gainsford, G. J.; Larese, J. Z.; Schramm, V. L.; Almo, S. C. *Biochemistry* **2001**, *40*, 853. (b) Miles, R. W.; Tyler, P. C.; Furneaux, R. H.; Bagdassarian, C.; Schramm, V. L. *Biochemistry* **1998**, *37*, 8615.
(4) Iminosugars: Recent Insights Into Their Bioactivity and Potential As Therapeutic Agents. In *Current Topics in Medicinal Chemistry*; Martin, O. R., Compain, P., Eds.; Bentham: Hilversum, The Netherlands, 2003; Vol. 3, Issue 5.
(5) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Curr. Top. Med. Chem.* **2003**, *3*, 561.
(6) Van der Spoel, A. C.; Jeyakumar, M.; Butters, T. D.; Charlton, H. M.; Moore, H. D.; Dwek, R. A.; Platt, F. M. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 17173

10.1021/ol035117h CCC: $25.00
Published on Web 08/02/2003

finding of more selective/potent inhibitors. Recently, we reported a general strategy for the practical synthesis of nojirimycin *C*-glycosides and analogues bearing an olefinic group at C-1 (Scheme 1).[7] Starting from these advanced

Scheme 1

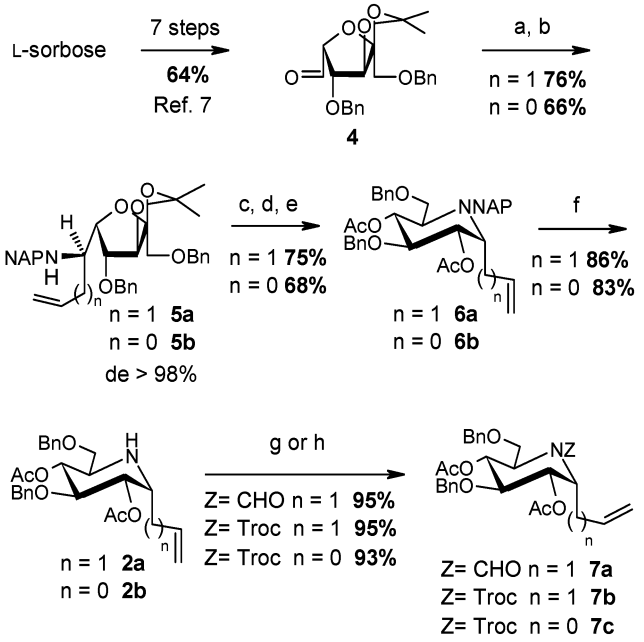


intermediates, we investigated olefin cross-metathesis[8] as a powerful methodology to a wide range of functionalized iminosugar-based building blocks. These extended glycomimetics can be further transformed into neoglycoconjugates mimicking glycoproteins, glycolipids, and sugar nucleotides, as well as into dendrimers.

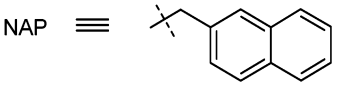
Although ruthenium-carbene catalysts have been widely used in carbohydrate chemistry for ring-closing metathesis,[9] there are relatively few examples of selective cross-metathesis.[10] Taking into account the concomitant self-metathesis reactions, the number of unproductive catalytic pathways, and the reversibility of all reactions involved, selective cross-metathesis of two complex alkene derivatives containing various functional groups represents a great challenge in organic synthesis. In the case of iminosugars, an additional issue is the presence of the endocyclic amino function that could potentially chelate the metal center and thus form unproductive complexes. First attempts to perform cross-metathesis reactions with Grubbs catalyst (**3**) using **1** or its hydrochloride salts[11] failed under various experimental conditions. The replacement of the endocyclic amine by a less coordinating function required finding experimental conditions for the selective and efficient deprotection of the endocyclic tertiary amine. After various attempts, it was found that the *N*-benzyl group in **1** could be removed by using 4 equiv of CAN in a two-phase system (THF/H_2O)[12] in 35−50% yield to furnish the iminosugar **2a** (Scheme 1).

This unsatisfactory process prompted us to find a new protective group for the endocyclic amine that could be selectively removed in the presence of benzyloxy groups and that would be resistant to the strongly acidic conditions needed for the cleavage of the acetal function.[13] To achieve this aim, we applied successfully our initial synthetic strategy[7] to the 2-naphthalenemethyl (NAP)[14] protected imine obtained from **4** instead of the corresponding *N*-benzyl derivative (Scheme 2). Condensation of aldehyde **4**, obtained

Scheme 2[a]



[a] Reagents and conditions: (a) $NAPNH_2$ (1.05 equiv), CH_2Cl_2, molecular sieves, 4 °C, 2 h. (b) AllMgBr or vinylMgBr (3 equiv), ether, 0 to 20 °C, 24 h. (c) TFA/H_2O (9/1), 30 h. (d) $NaBH_3CN$ (4 equiv), AcOH (1 equiv), MeOH, 30 h. (e) Ac_2O (6 equiv), Py, 5 h. (f) DDQ (3 equiv), CH_2Cl_2/MeOH, 1 h. (g) HCOONa (2.5 equiv), PivCl (2.5 equiv), CH_2Cl_2, 8 h. (h) TrocCl (1.5 equiv), Py, 2 h.



in seven steps and 64% yield from L-sorbose,[7a] with 2-naphthalenemethylamine afforded the corresponding imine, which was reacted with allyl- or vinylmagnesium bromide to give the diastereomerically pure amines **5** after purification by flash chromatography. The three-step sequence of deprotection of the acetal function, intramolecular reductive amination, and acylation of the resulting piperidinols afforded the expected protected nojirimycine *C*-glycosides **6** in good

(7) (a) Godin, G.; Compain, P.; Masson, G.; Martin, O. R. *J. Org. Chem.* **2002**, *67*, 6960. (b) Masson, G. Compain, P.; Martin, O. R. *Org. Lett.* **2000**, *2*, 2971.

(8) For a recent review about olefin cross-metathesis see: Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900.

(9) (a) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519. (b) Jorgensen, M.; Hadwiger, P.; Madsen, R.; Stütz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565.

(10) See for example: (a) Roy, R.; Dominique, R.; Das, S. *J. Org. Chem.* **1999**, *64*, 5408. (b) 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. (c) Plettenburg, O.; Mui, C.; Bodmer-Narkevitch, V.; Wong, C.-H. *Adv. Synth. Catal.* **2002**, *344*, 622. (d) Dondoni, A.; Giovanni, P. P.; Marra, A. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2380. (e) Biswas, K.; Coltart, D. N.; Danishefsky, S. J. *Tetrahedron Lett.* **2002**, *43*, 6107.

(11) Rambaud, L.; Compain, P.; Martin, O. R. *Tetrahedron: Asymmetry* **2001**, *12*, 1807 and references cited therein.

(12) Cipolla, L.; Palma, A.; La Ferla, B.; Nicotra, F. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2161.

(13) In our case, *N*-allyl or *N*-PMB groups were found to be partially or totally cleaved during the deprotection of the acetal function in aqueous TFA.

(14) Gaunt, M. J.; Yu, J.; Spencer, J. B. *J. Org. Chem.* **1998**, *63*, 4172.

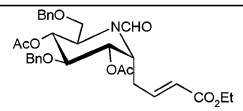
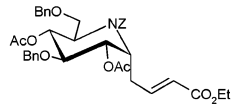
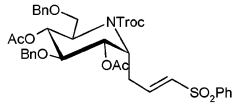
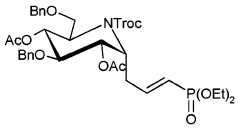
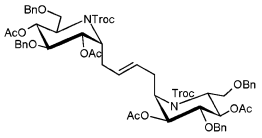
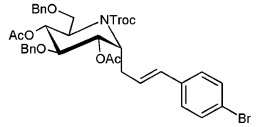
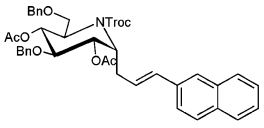
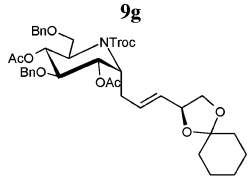
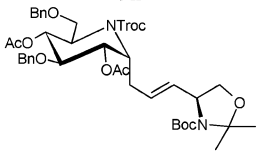
yields and high diastereoselectivities. The *N*-naphthalenemethyl protective group was selectively and efficiently removed in the presence of 3 equiv of DDQ,[15] and the resulting secondary amines **2a**,**b** were formylated[16] or protected with a Troc group to provide iminosugars **7** in 77−82% yield for the two steps.

Starting from α-1-*C*-allyl-1-deoxynojirimycin analogues **7a**,**b**, the cross-metathesis reaction was first investigated with α,*β*-unsaturated ester, sulfone and phosphonate **8a**−**c** (Table 1, entries 1−4). These alkenes were chosen because of the utility of their functions as reagents or chemical intermediates. For example, *δ*-amino esters **9a**,**b** may be regarded as sugar amino acid (SAA) mimics: such compounds are useful building blocks for the assembly of oligosaccharide- or peptide-mimetic libraries;[17] phosphonate **9d** is an advanced precursor of sugar nucleotide analogues. In a typical experimental procedure, a solution of **7** (0.06 M in dichloromethane) was refluxed in the presence of 2−3 equiv of **8** and 5−10 mol % Grubbs catalyst (**3**) for 20 h. Under these conditions, the expected iminosugars *C*-glycosides **9a**−**d** were obtained in 50−96% yield and with excellent stereoselectivity, as the (*E*)-stereoisomer was the only product detected by NMR spectroscopy. The lower yields obtained for compounds **9c** and **9d** were due to homodimerization of **7b** (**9e** was isolated in around 25% yield in both cases). Iminosugar **7b** was independently homodimerized to give efficiently the pseudodisaccharide **9e** in 85% yield (entry 5). The cross-metathesis reaction was also performed with aromatic olefins **8d**,**e**. The reaction of **7b** with 3 equiv of 4-bromostyrene **8d** led to the formation of the expected product **9f** in 45% yield together with 52% yield of homodimer **9e**. Dimerization of the iminosugar moiety could be suppressed successfully by using 5 equiv of the aromatic olefin as was shown with 2-vinylnaphthalene (Table 1, entry 7). Another powerful application of this methodology is to provide C-linked pseudoglycolipids or glycopeptides[18] that can be used for the synthesis of biorelevant glycoconjugate mimetics or as building blocks in combinatorial synthesis.[19]

The metathesis reaction between **7b** and enantiopure protected diol **8f** or oxazolidine **8g** led to the formation of the expected iminosugar *C*-glycosides **9h**,**i** in high yields (entries 8 and 9). The *N*-Troc protecting group of iminosugar **9b** was selectively removed using Zn in AcOH/ether[20] to yield the secondary endocyclic amine **10** that could be further functionalized to obtain potential glycosyltransferase inhibitors on the basis of a bisubstrate concept[2] (Table 1, entry 2).

To further explore the scope and generality of this method, the cross-metathesis reaction was performed with the *β*-1-*C*-vinyl-1-deoxynojirimycin derivative **15** and its α-epimer analogue **7c**. The fully protected *β*-configured iminosugar **15** was synthesized in seven steps and 30% overall yield from aldehyde **4** (Scheme 3). Previous studies in our group

Table 1. Ruthenium-Catalyzed Cross-Metathesis of Imino-*C*-glycoside **7** with Olefin **8** Using 10 Mol % **3**

Entry	**7**	**8** (eq.)	product[a]	yield (%)[b]
1	**7a**	 **8a** (3)	 **9a**	96[c]
2	**7b**	 **8a** (3)	 **9b** g → **10**	92
3	**7b**	 **8b** (3)	 **9c**	50[d]
4	**7b**	 **8c** (2)	 **9d**	71[d]
5	**7b**	–	 **9e**	85
6	**7b**	 **8d** (3)	 **9f**	45[e]
7	**7b**	 **8e** (5)	 **9g**	90[f]
8	**7b**	 **8f** (5)	 **9h**	88[f]
9	**7b**	 **8g** (5)	 **9i**	87[f]

[a] *E*/*Z* > 20/1. [b] Isolated yield. [c] Performed with 5 mol % catalyst **3** relative to **7a**. [d] Dimer **9e** (25%) was also isolated. [e] Dimer **9e** (52%) was also isolated. [f] Performed with 20 mol % catalyst **3** relative to **7b**. [g] Zn (30 equiv), Et_2O/AcOH (2/1), 3 h, 90%.

(15) (a) Xia, J.; Abbas, S. A.; Locke, R. D.; Piskorz, C. F.; Alderfer, J. L.; Matta, K. L. *Tetrahedron Lett.* **2000**, *41*, 169. (b) Wright, J. A.; Yu, J.; Spencer, J. B. *Tetrahedron Lett.* **2001**, *42*, 4033.

(16) Bringmann, G.; Ochse, M.; Michel, M. *Tetrahedron* **2000**, *56*, 581.

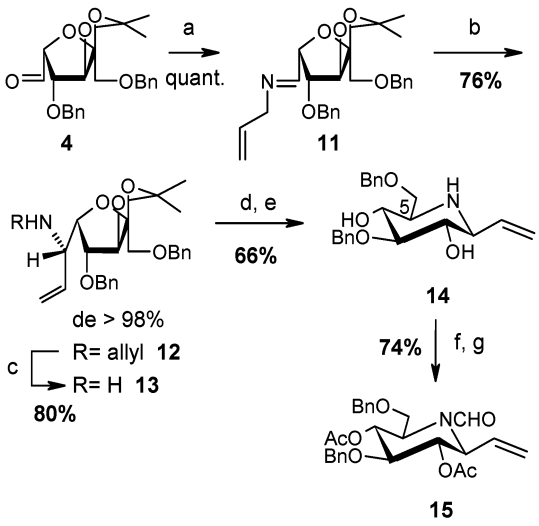
(17) Gruner, S. A. W.; Locardi, E.; Lohof, E.; Kessler, H. *Chem. Rev.* **2002**, *102*, 491.

(18) Dondoni, A.; Marra, A. *Chem. Rev.* **2000**, *100*, 4395.

(19) Schweizer, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 230.

(20) Endo, A.; Yanagisawa, A.; Abe, M.; Tohma, S.; Kan, T.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 6552.

Scheme 3[a]



[a] Reagents and conditions: (a) $AllylNH_2$ (1.1 equiv), CH_2Cl_2, molecular sieves, 4 °C, 2 h. (b) VinylMgBr (3 equiv), ether, 0 to 20 °C, 24 h. (c) $Pd(PPh_3)_4$, NDMBA (2.1 equiv), CH_2Cl_2, 35 °C, 3 h. (d) TFA/H_2O (9/1), 36 h. (e) $NaBH_3CN$ (4 equiv), AcOH (1 equiv), MeOH, 24 h. (f) HCOONa (2.5 equiv), PivCl (2.5 equiv), CH_2Cl_2, 8 h. (g) Ac_2O (6 equiv), Py, 16 h.

indicated that the amine function of the sorbofuranose **12** had to be deprotected before the reductive amination step to obtain high stereocontrol at C-5. Allylamine was used as a temporary nitrogen protecting group. Diastereoselective chain extension of *N*-allylimine **11** with vinylmagnesium bromide afforded the expected primary amine **13** after deprotection under classical conditions.[21] Intramolecular reductive amination of the aminosorbose hemiketal liberated upon acidic hydrolysis of the isopropylidene group provided the diastereomerically pure pseudo-β-D-gluco product **14**. N-Formylation of the endocyclic amine followed by acylation of the hydroxyl groups at C-2 and C-4 afforded the protected β-1-*C*-vinyl-1-deoxynojirimycin analogues **15**.

In sharp contrast with findings for α-1-*C*-allyl-1-deoxynojirimycin analogues **7a**,**b**, exposure of β-1-*C*-vinyl derivative **15** to various olefins (**8a**,**c**,**d**,**g**) using 5−20 mol % Grubbs catalyst (**3**) led to almost complete recovery of the starting material (less than 5% conversion according to ^1H NMR and mass spectroscopy). In addition, attempts to perform ruthenium-catalyzed cross-metathesis of α-1-*C*-vinyl derivative **7c** with ethyl acrylate (**8a**) or its self-metathesis reaction proved to be unsuccessful. These results may be reasonably explained by greater Ru−O chelation possibilities[8] and increased steric hindrance due to close proximity of the reacting alkene and the bulky iminosugar moiety.[22]

In conclusion, we have reported the first example of cross-metathesis reactions with iminosugar *C*-glycosides. The results obtained from α-1-*C*-allyl-1-deoxynojirimycin analogues **7a**,**b** demonstrated the simplicity and the power of cross-metathesis reaction to rapidly generate iminosugar *C*-glycosides with a great degree of structural diversity in the aglycon moieties. This practical and selective methodology provides new avenues for the synthesis of glycoconjugate mimetics of biological interest. Efforts toward this aim are currently in progress in our laboratory.

Acknowledgment. Financial support of this study by grants from CNRS and the association "Vaincre les Maladies Lysosomales" is gratefully acknowledged. G.G. thanks the council of *Région Centre* and the CNRS for a fellowship.

Supporting Information Available: ^1H and ^{13}C NMR spectra data for selected compounds (**2a**, **2b**, **5b**, **6a**, **7b**, **9b**, **9d**, **9f**, **9h**, **9i**, **10**, and **12**−**14**) and selected experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035117H

(21) Garro-Helion, F.; Merzouk, A.; Guibe, F. *J. Org. Chem.* **1993**, *58*, 6109.

(22) For related examples with 1-*C*-vinyl glycoside, see: (a) Roy, R.; Das, S. K.; Dominique, R.; Trono, M. C.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *Pure Appl. Chem.* **1999**, *71*, 565. (b) Nolen, E. G.; Kurish, A. J.; Wong, K. A.; Orlando, M. D. *Tetrahedron Lett.* **2003**, *44*, 2449.