ORGANIC LETTERS

2004
Vol. 6, No. 22
3961−3964

Metathesis of Structurally Preorganized Bivalent Carbohydrates. Synthesis of Macrocyclic and Oligomeric Scaffolds

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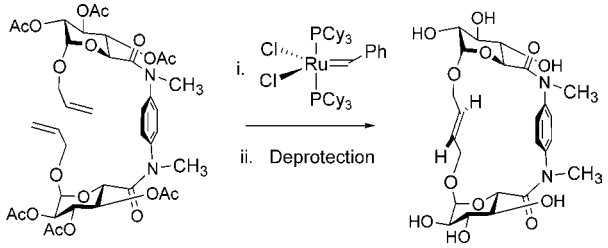
Received August 9, 2004

ABSTRACT



Bivalent carbohydrate substrates for metathesis were synthesized from glucuronic acid and phenylene-1,4-diamine. The substrate secondary structure depends on whether secondary or tertiary amides are present, and this influences the course of the metathesis reaction leading to novel multivalent scaffolding. Molecular modeling suggests that a very rigid macrocyclic scaffold has potential for the development of α-helix peptidomimetics.

Monosaccharides have been introduced and validated as biologically relevant scaffolds for the presentation of pharmacophore groups to receptors.[1] Advantages of using saccharides are that they display a high density of functional groups, are available as single enantiomers, and contain multiple sites for attachment of recognition groups (multivalent or multifunctional scaffolds).[2] The development of rigid bivalent saccharide scaffolds with well-defined 3D structure is of interest to us.[3] Ultimately, recognition groups or molecules will be grafted onto the scaffolds; this will give novel monovalent and multivalent ligands[4] for biological evaluation.

Scaffolds comprised of secondary and tertiary amides derived from two D-glucuronic acid units which are bridged by 1,4-phenylenediamine (e.g., **1** and **2**) have been synthesized recently.[5] The topology of the glucuronic acid residues in **1** and **2** depends on the structure of the amide: the secondary amides in **1** prefer the *Z*-configuration (Figure 1),[6] whereas the tertiary amides in **2** prefer *E*-configuration (Figures 1 and 2). The X-ray crystal structure of **2** (**2d**, R = Ac, Figure 2) showed that one of its amides was *E-anti* whereas the other was *E-syn* and the carbohydrates stacked in a *cis* or U-shaped conformation.[7] Qualitative NOE studies for **2** in solution (in D_2O for R = H; in $CDCl_3$ for R = Ac)

(1) Hirschmann, R.; Nicolaou, K. C.; Pietranico, S.; Salvino, J.; Leahy, E. M.; Sprengeler, P. A.; Furst, G.; Smith, A. B., III; Strader, C. D.; Cascieri, M. A.; Candelore, M. R.; Donaldson, C.; Vale, W.; Maechler, L. *J. Am. Chem. Soc.* **1992**, *114*, 9217. (b) Nicolaou, K. C.; Salvino, J. M.; Raynor, K.; Pietranico, S.; Reisine, T.; Freidinger, R. M.; Hirschmann, R. In Peptides—Chemistry, Structure, and Biology. *Proceedings of the 11th American Peptide Symposium*; Rivier, J. E., Marshall, G. R., Eds.; ESCOM: Leiden, 1990; pp 881−884.

(2) Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2503.

(3) Bradley, H.; Fitzpatrick, G.; Glass, W. K.; Kunz, H.; Murphy, P. V. *Org. Lett.* **2001**, *3*, 2629. (b) Murphy, P. V.; Bradley, H. Tosin, M.; Pitt, N.; Fitzpatrick, G. M. Glass, W. K. *J. Org. Chem.* **2003**, *68*, 5693.

(4) Mammen, M.; Choi, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754.

(5) Tosin, M.; Müller-Bunz, H.; Murphy, P. V. *Chem. Commun.* **2004**, 494.

(6) The *Z*-hydrogen-bonded and *Z*-anti conformations (Figure 1) have been observed for such secondary amides in X-ray crystal structures. Tosin, M.; O'Brien, C.; Murphy, P. V. Private communication.

10.1021/ol0484254 CCC: $27.50
Published on Web 10/02/2004

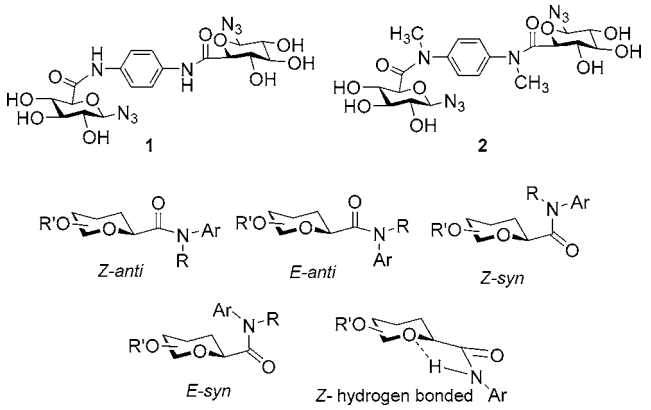


Figure 1. Amide structure and nomenclature.

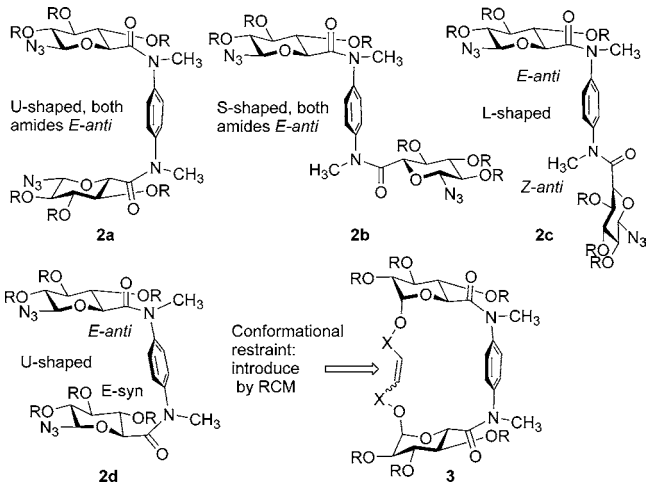
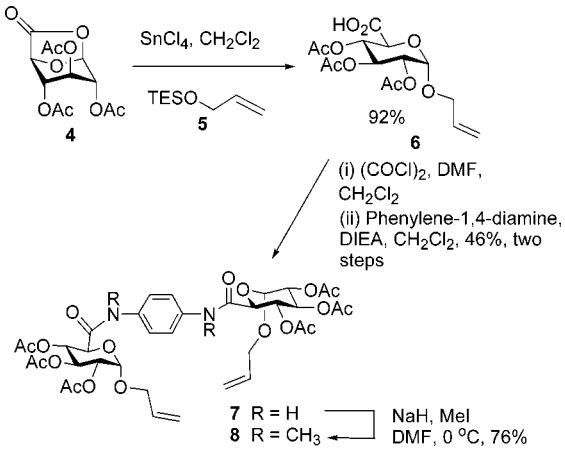


Figure 2. Conformational and configurational isomers of **2**[5] and design of constrained scaffold **3**.

indicate that the amides prefer *E-anti* conformations; this can be represented by *cis* or U-shaped conformation **2a** and/or the *trans* or S-shaped conformation **2b**. There is also evidence for the presence of an L-shaped isomer **2c** (<15%).[8] Alkylation and dealkylation of the amide form a basis to alter the topology or structural space occupied by the sugars and thus to alter spatial presentation of groups attached to the sugars. We envisaged that macrocyclic compounds,[9] such as **3**, composed of two sugar units could be prepared by ring closing metathesis[10] (RCM) of substrates containing tertiary amides.

The synthesis of substrates to explore this possibility was carried out. Glycosidation of the 6,1-lactone donor **4**[11] promoted by tin(IV) chloride is known to give α-glycosides with high stereoselectivity[12] and efficiency if an appropriate silyl ether is used as an acceptor.[10] The reaction of **4** with the TES[13] derivative **5** thus gave **6** in 92% yield. This carboxylic acid was then converted into its acid chloride and a subsequent reaction with 1,4-phenylenediamine gave the secondary amide substrate **7**. Methylation of the amides of **7** using sodium hydride and methyl iodide in DMF at 0 °C gave **8** (Scheme 1).

Scheme 1. Synthesis of Metathesis Substrates



Reaction of **7** (Scheme 2) with the Grubbs' catalyst[14] gave linear oligomers **9** and **10** as a result of cross metathesis processes as well as macrocycle **11**.[15] In situ RCM of either **9** or **10** explains the origin of **11**.[16] The constraint imposed by the presence of *Z*-configured amides prevents formation of a macrocycle containing only two saccharides. The behavior of the tertiary amide **8** in the presence of the Grubbs' catalyst contrasted with that of **7** (Scheme 3); the alteration of amide configuration[17] preorganized the alkenes[18] so that RCM occurred and gave dimeric macrocycle **12** as

(7) The U-shaped or *cis* or *syn* conformation is defined as the carbohydrate groups being on same side of plane defined by aromatic ring; the S-shaped or *trans* or *anti* conformation have the carbohydrates on opposite sides of the ring.

(8) The ^{1}H NMR spectrum for **2** shows two signal sets due to amide bond rotamers: the first set (major structural isomer) is assigned to **2a** and/or **2b**; the second set is assigned to isomer **2c** or a related *syn* conformer (not shown).

(9) For an example of conformationally unbiased macrocyclisation by RCM, see: Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942.

(10) For a review of application of metathesis in glycobiology, see: Leeuwenburgh, M. A.; van der Marel, G. A.; Overkleeft, H. S. *Curr. Opin. Chem. Biol.* **2003**, *7*, 757.

(11) (a) Tosin, M.; Murphy, P. V. *Org. Lett.*, **2002**, *4*, 3675−78. (b) Poláková, M.; Pitt, N.; Tosin, M.; Murphy, P. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 2518.

(12) The origin of the stereoselectivity from **4** and related donors is currently being investigated. Murphy, P. V.; Poláková, M.; Pitt, N.; Tosin, M. 22nd International Carbohydrate Symposium, Glasgow, UK, July 23rd-27, 2004, C44.

(13) The TES ether was prepared as it has a higher boiling point than the TMS ether which simplified isolation and purification.

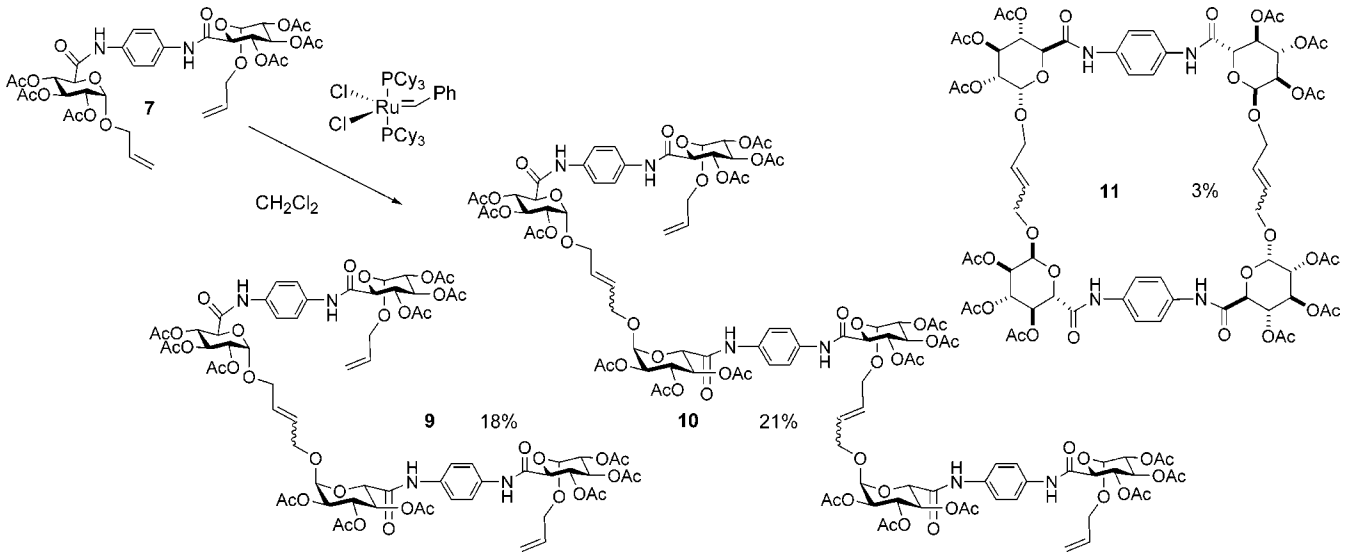
(14) (a) Nguyen, S. T.; Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−20. (b) Johnson, L. K.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 3974.

(15) The products from these reactions were hydrogenated using Pd−C and H_2. The analytical data for the reduced products is provided in the Supporting Information.

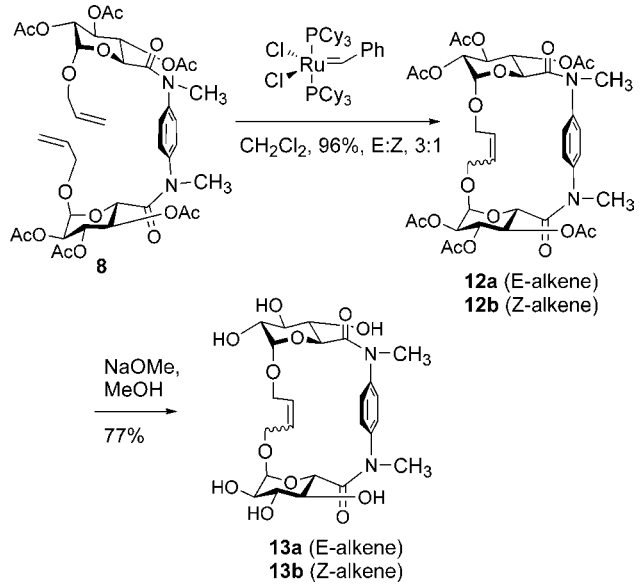
(16) Cross metathesis followed by ring-closing metathesis has been observed previously. Smith, A. B.; Adams, C. M.; Kozmin, S. A.; Paone, D. V. *J. Am. Chem. Soc.* **2001**, *123*, 5925.

(17) The 2D NOE spectrum of **8** showed a strong cross-peak between the signal for aromatic protons and that of the H-5 proton of the glucuronic acid residue but not between H-5 and the methyl group, consistent with a preferred *E-anti* conformation for amides of **8**.

Scheme 2. Metathesis of **7**



Scheme 3. Metathesis of **8**



the only product (96%, *E*/*Z* alkene ratio = 3:1); this was converted to **13** by removal of the protecting groups.[19]

The carbohydrate topology in macrocycles **12** and **13** is structurally more constrained than those in **2** and **8**. The ^{1}H NMR spectra of both alkene isomers **13a** (*E*-alkene) and **13b** (*Z*-alkene) shows one signal set. The constraint imposed by macrocyclization does not allow access to an isomer where one amide has the *Z*-amide configuration (similar to **2c**). Also precluded for **12** and **13** are *E-syn* conformations (similar to **2d**).

The structural conclusions were supported by use of conformational searching techniques (Macromodel 8.5[20]) to locate the low energy conformers for **13a** (*E*-alkene); the only structures which were obtained from these calculations had *E-anti* amides. The lowest energy structures were conformers where the alkene group was oriented either parallel or perpendicular to the aromatic ring;[21] when the parallel arrangement occurred the distance between the alkene and aromatic groups is ~4.5 Å. The S-shaped conformation (similar to **2b**) is more than 20 kJ/mol higher in energy than the lowest energy U-shaped structure (similar to **2a**). The structural assignment was supported by both qualitative NOESY and ROESY studies (Figure 3).[22]

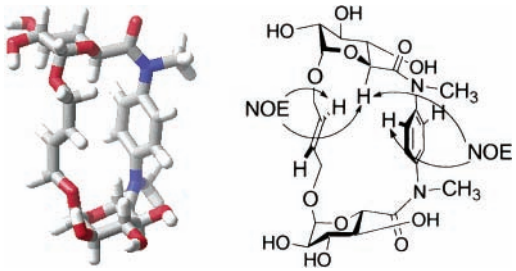


Figure 3. Lowest energy structure and selected NOE enhancements observed for **13a** (*E*-alkene).

Monosaccharides, such as β-D-glucopyranoside, have been shown to be scaffolds suitable for the development of non-peptide containing mimetics of the β-turn.[1] We have examined, by molecular modeling, the structural relationship of **13a** to the α-helix peptide backbone in order to determine if there is potential for peptidomimetic design.[23] The preliminary molecular modeling (Figure 4) study indicated

(18) For a previous example of copper promoted preorganization of olefins for RCM, see: Weck, M.; Mohr, B.; Sauvage, J.-P.; Grubbs, R. H. *J. Org. Chem.* **1999**, *64*, 5463.

(19) The alkenes were separated by HPLC.

(20) Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

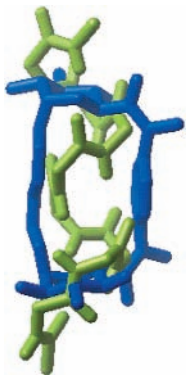


Figure 4. Superimposition of **13a** (blue, hydrogen atoms not shown) and the backbone of an α-helical peptide (green, polar hydrogens only shown). The following atom pairs were superimposed to generate the overlapped structures: C-α of residue i and glucuronic acid O-2; C-α of residue i+1 and glucuronic acid O-4; C-α of residue i+2 and nitrogen; C-α of residue i+5 and nitrogen; C-α of residue i+6 and glucuronic acid O-4; C-α of residue i+7 and glucuronic acid O-2.

that it may be possible to use the O-2 and O-4 atoms of the saccharides and the nitrogen atoms of the phenylenediamine unit to project side chains of amino acids in orientations that may correspond to those projected from the C_α of residues i, i+1, i+2, i+5, i+6, and i+7 of a helical peptide backbone (Figure 4).[24]

In summary, we have described the synthesis of new macrocycles and oligomers from appropriately preorganized glycocluster based substrates. Molecules described herein, which have well-defined 3D structural features, could be considered to be related to nonnatural oligomers with well-defined secondary structural features. These properties have been identified as of interest in development of novel biomimetic therapeutics and/or functional materials.[25] One possibility for macrocycle **13a** would be to explore its potential as a scaffold for development of novel peptidomimetics or for the display of multiple carbohydrate ligands with well-defined structure; these studies are in progress.

Acknowledgment. The research was funded under the Program for Research in Third-Level Institutions (PRTLI), administered by the HEA (of Ireland) and by the European Commission (MEIF-CT-2003-500748). P.V.M. thanks Science Foundation Ireland for a Program Investigator Grant Award.

Supporting Information Available: Experimental description and analytical data, spectra. Molecular modeling files including pdb files for structures in Figures 3 and 4 and coordinate files for low energy structures of **13a** compatible with Maestro/Macromodel. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) Low energy structures were obtained by a conformational search with Macromodel 8.5. All low energy structures within 20 kJ/mol of the global minimum were retained. Only *E-anti* conformers with the U-shaped structure were found and this included isomers with the alkene either parallel or perpendicular to the aromatic ring. The coordinates for low energy structures are provided as Macromodel dat files as Supporting Information.

(22) **ROE Spectroscopy of 12a.** Data were collected on Varian 300 and 500 MHz spectrometers. Macrocycle **12a** (1.9 mg) was dissolved in 0.7 mL of D_2O. The signals were first assigned with standard Varian gradient COSY experiments at 25 °C. A two-dimensional Tr-ROESY experiment (spin-lock field of 2.2 kHz with mixing time of 0.5 s, at 30 °C) was used to obtain the 2D ROESY spectrum.

(23) Hirschmann, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1278. (b) Bursavich, M. G.; Rich, D. H. *J. Med. Chem.* **2002**, *45*, 541. (c) Hruby, V. J. *Acc. Chem. Res.* **2001**, *34*, 389.

(24) For a recent example on development of an α-helical peptide mimic, see: Yin, H.; Hamilton, A. D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1375.

(25) Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893.