ORGANIC LETTERS

2003
Vol. 5, No. 9
1475−1478

Nitrone Cycloadditions to Isolevoglucosenone: Ready Access to a New Class of Directly Linked (1→3)-Imino-*C*-disaccharides

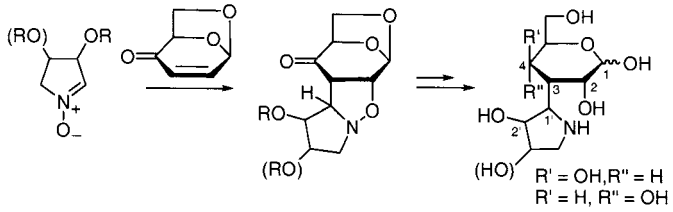
Francesca Cardona,* Andrea Goti, and Alberto Brandi

Dipartimento di Chimica Organica "Ugo Schiff", Polo Scientifico, Università di Firenze, via della Lastruccia 13, I-50019 Sesto Fiorentino, Firenze, Italy

francesca.cardona@unifi.it

Received February 12, 2003

ABSTRACT



Straightforward access to a new class of D-gulo- and D-allo-derived directly linked (1→3)-imino-*C*-disaccharides by means of cycloaddition reactions of enantiopure polyhydroxylated pyrroline *N*-oxides with isolevoglucosenone is reported. The cycloaddition reactions display a high level of double asymmetric induction, which allows a partial kinetic resolution of a racemic nitrone.

Iminosugars have recently attracted a great deal of interest due to their ability to inhibit glycosidases[1] and hence their enormous potential in application in the treatment of numerous pathologies such as diabetes,[2] viral infections,[3] and cancer.[4]

Glycosidases display aglycon specificity in that they recognize oligosaccharides having subtle differences in the aglycon portion and glycosidic linkage. In this respect, it has been postulated[5] that glycosidase inhibitors able to interact with the aglycon binding site may show increased potency and selectivity.

Compounds bearing an additional C-substituent (particularly a sugar) at the pseudoanomeric center linked through a nonhydrolyzable bond (such as imino-*C*-disaccharides) can mimic the aglycon part of an oligosaccharide. For this reason, several syntheses of imino-*C*-disaccharides have been reported,[6−8] and some of these compounds have shown significant biological activities.[6c,d,7d]

Structural diversity is of extreme importance in order to get information about structure−activity relationship. Thus, synthetic efforts have regarded the preparation of compounds

(1) *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999.

(2) See, e.g.: (a) Horii, S.; Fukase, H.; Matsuo, T.; Kameda, Y.; Asano, N.; Matsui, K. *J. Med. Chem.* **1986**, *29*, 1038−1046. (b) Elbein, A. D. *Annu. Rev. Biochem.* **1987**, *56*, 497−594.

(3) See, e.g.: (a) Karlsson, G. B.; Butters, T. D.; Dwek, R. A.; Platt, F. M. *J. Biol. Chem.* **1993**, *268*, 570−576. (b) Fenouillet, E.; Papandreou, M.-J.; Jones, I. M. *Virology* **1997**, *231*, 89−95.

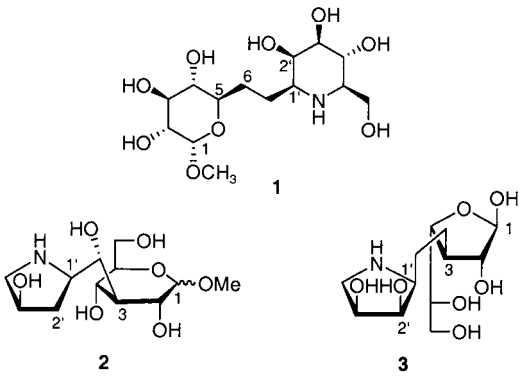
(4) See, e.g.: (a) Humphries, M. J.; Matsumoto, K.; White, S. L.; Olden, K. *Cancer Res.* **1986**, *46*, 5215−5222. (b) Goss, P. E.; Baptiste, J.; Fernandes, B.; Baker, M.; Dennis, J. W. *Cancer Res.* **1994**, *54*, 1450−1457.

(5) (a) Legler, G. In *Carbohydrate Mimics*; Chapleur, Y., Ed; Wiley-VCH: Weinheim, Germany, 1998; pp 461−490. (b) Martin, O. R. In *Carbohydrate Mimics. Concepts and Methods*; Chapleur, Y., Ed; Wiley-VCH: Weinheim, Germany, 1998; p 259.

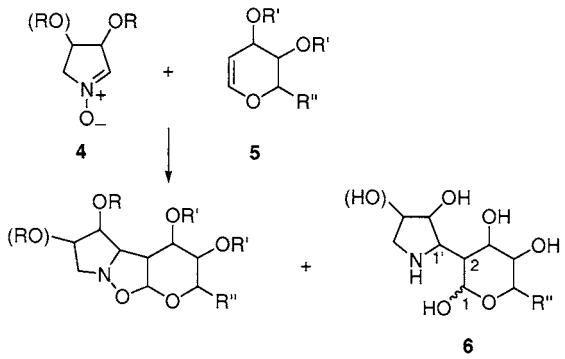
(6) (a) Johnson, C. R.; Miller, M. W.; Golebiowski, A.; Sundram, H.; Ksebati, M. B. *Tetrahedron Lett.* **1994**, *35*, 8991−8994. (b) Martin, O. R.; Liu, L.; Yang, F. *Tetrahedron Lett.* **1996**, *37*, 1991−1994. (c) Johns, B. A.; Pan, Y. T.; Elbein, A. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 4856−4865. (d) Leeuwenburgh, M. A.; Picasso, S.; Overkleeft, H. S.; van der Marel, G. A.; Vogel, P.; van Boom, J. H. *Eur. J. Org. Chem.* **1999**, *1185*, 5−1189. (e) Duff, F. J.; Vivien, V.; Wightman, R. H. *Chem. Commun.* **2000**, 2127−2128. (f) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203−7214.

10.1021/ol0342507 CCC: $25.00
Published on Web 04/09/2003

of different structures such as "linear" (1→6)- and (1→5)-C-linked iminodisaccharides[6] (e.g., **1**[6a]), "branched" (1→1)-, (1→2)-, (1→3)-, and (1→4)-C-linked iminodisaccharides[7,6c] (e.g., **2**[7g]), and homo-C-linked iminodisaccharides[8] (e.g., **3**[8b]), in which the imino sugar is linked to the monosaccharide by a two carbon linker.

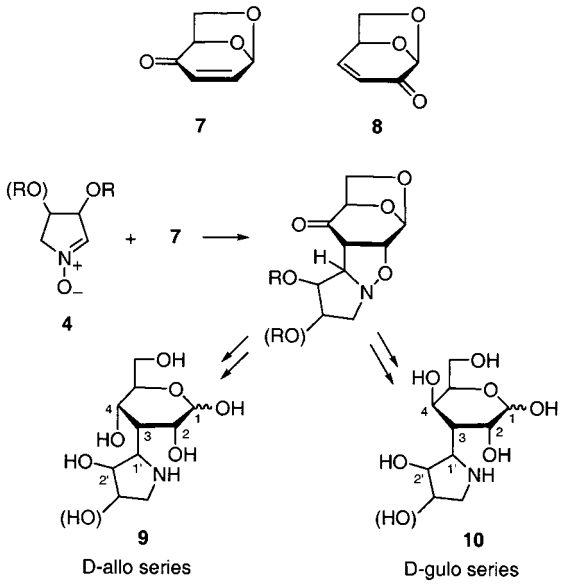


In this field, we have recently synthesized (1→2)-linked pseudo imino-*C*-disaccharides **6**, where the iminosugar is directly linked at C-2 of monosaccharides.[9,10] The synthetic approach was based on highly selective 1,3-dipolar cycloadditions of enantiopure polyhydroxylated pyrroline *N*-oxides **4** with 1,2-glycals **5**, followed by simple elaborations of the adducts.[9,10] The major limitation of the process was the low reactivity of nitrones toward glycals in the crucial cycloddition step, which forced us to use a 3 equiv excess of glycal, high temperatures, and long reaction times. The problem was partially resolved by performing the cycloaddition reactions at high pressure.[11]



In this Letter, we report a straightforward access to a new class of directly linked (1→3)-imino-*C*-disaccharides belonging to D-allo and D-gulo series (**9** and **10**, respectively) by means of cycloaddition reactions between enantiopure polyhydroxylated pyrroline *N*-oxides **4** and isolevoglucosenone (**7**).[12]

We envisaged that isolevoglucosenone (**7**) could be an excellent dipolarophile in 1,3-dipolar cycloadditions to nitrones. Indeed, the presence of the activated double bond should ensure high reactivity and regioselectivity.



To our knowledge, the use of **7** in cycloaddition reactions has no precedent in the literature. In contrast, cycloaddition reactions of isomeric levoglucosenone (**8**)[13] to nitrones and nitrile oxides have been reported by Paton and co-workers.[14]

Both **7** and **8** are C_6 chiral building blocks that are extremely attractive from a synthetic point of view, since they contain the information of a saccharide unit blocked in the 1,6-anhydro bridge, which avoids the use of protecting groups at C-1 and C-6 OH. Furthermore, the bridge sterically hinders the β-face of both molecules, forcing the reactions to occur on the α-face (the *exo* face), usually with a high degree of stereoselectivity. Their use in the syntheses of imino-*C*-disaccharides has been exploited by Vogel and coworkers.[7e,g,i,8]

Isolevoglucosenone (**7**), readily derived from D-glucose in four synthetic steps,[15,16] was reacted with 1 equiv of

(7) (a) Frérot, E.; Marquis, C. Vogel, P. *Tetrahedron Lett.* **1996**, *37*, 2023−2026. (b) Baudat, A.; Vogel, P. *Tetrahedron Lett.* **1996**, *37*, 483−484. (c) Baudat, A.; Vogel, P. *J. Org. Chem.* **1997**, *62*, 6252−6260. (d) Kraehenbuehl, K.; Picasso, S.; Vogel, P. *Helv. Chim. Acta* **1998**, *81*, 1439−1479. (e) Zhu, Y.-H.; Vogel, P. *Chem. Commun.* **1999**, 1873−1874. (f) Marquis, C.; Picasso, S.; Vogel, P. *Synthesis* **1999**, 1441−1452. (g) Zhu, Y.-H.; Vogel, P. *J. Org. Chem.* **1999**, *64*, 666−669. (h) Cheng, X.; Kumaran, G.; Mootoo, D. R. *Chem. Commun.* **2001**, 811−812. (i) Navarro, I.; Vogel. P. *Helv. Chim. Acta* **2002**, *85*, 152−160.

(8) (a) Cardona, F.; Robina, I.; Vogel, P. *J. Carbohydr. Chem.* **2000**, *19*, 555−571. (b) Marquis, C.; Cardona, F.; Robina, I.; Wurth, G.; Vogel, P. *Heterocycles* **2002**, 56, 181−208.

(9) Cardona, F.; Valenza, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1997**, *38*, 8097−8100.

(10) Cardona, F.; Valenza, S.; Picasso, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1998**, *63*, 7311−7318.

(11) Cardona, F.; Salanski, P.; Chmielewski, M.; Valenza, S.; Goti, A.; Brandi, A. *Synlett* **1998**, 1444−1446.

(12) For recently reported cycloadditions of nitrones **4** to sugar-derived α, β-unsaturated lactones, see: (a) Jurczak, M.; Rabiczko, J.; Socha, D.; Chmielewski, M.; Cardona, F.; Goti, A.; Brandi, A. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2015−2022. (b) Socha, D.; Jurczak, M.; Frelek, J.; Klimek, A.; Rabiczko, J.; Urbańczyk-Lipkowska, Z.; Suwińska, K.; Chmielewski, M.; Cardona, F.; Goti, A.; Brandi, A. *Tetrahedron*: *Asymmetry* **2001**, *12*, 3163−3172.

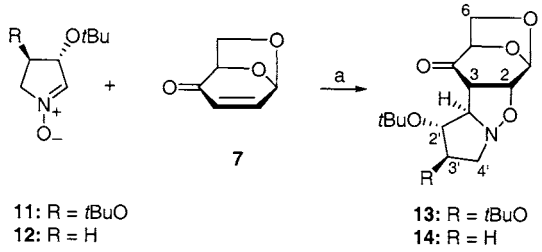
(13) *Levoglucosenone and Levoglucosans, Chemistry and Applications*; Witczak, Z. J., Ed.; ALT Press, Inc., Science Publishers: Mount Prospect, IL, 1994.

(14) (a) Blake, A. J.; Forsyth, A. C.; Paton, R. M. *J. Chem. Soc., Chem. Commun.* **1988**, 440−442. (b) Blake, A. J.; Cook, T. A.; Forsyth, A. C.; Gould, R. O.; Paton, R. M. *Tetrahedron* **1992**, *48*, 8053−8064.

(15) Horton, D.; Norris, P.; Roski, J. *J. Org. Chem.* **1996**, *61*, 3783−3793.

D-tartaric acid-derived nitrone **11**[17] in toluene at room temperature, affording after 1.5 h a single adduct **13** in 89% yield. Analogously, L-malic acid-derived nitrone **12**[18] afforded the sole adduct **14** (Scheme 1). Hence, the cycloadd

Scheme 1[a]



[a] Reaction conditions: (a) toluene, rt, 1.5−2.5 h; 89% for **13**, 89% for **14**.

dition reactions were completely regio- and stereoselective, as confirmed by ^{1}H NMR analysis of the crude reaction mixtures.

The unambiguous structure determination relies on spectral data, including two-dimensional COSY and NOESY NMR spectra. For instance, adduct **13** displayed cross-peaks between signal pairs at δ 4.36 (H-2) and 2.67 ppm (H-4′), δ 4.02 (H-2′) and 3.41 ppm (H-3), and δ 3.90 (H_{endo}-6) and 3.41 ppm (H-3) in the two-dimensional NOESY ^{1}H NMR spectrum. The single cycloaddition product isolated in both cases is the result of the preferred approach of the nitrones, in an *exo* fashion, to the lower face of isolevoglucosenone **7** (the α-face). By this approach (Figure 1), repulsive van der

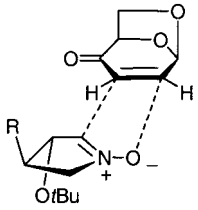
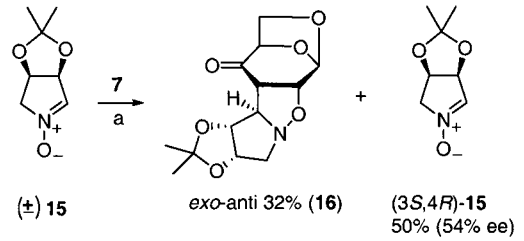


Figure 1. Preferred *exo* approach of nitrones **11** and **12** to the α-face of isolevoglucosenone (**7**), anti to the 1,6-anhydro bridge and the vicinal *t*-butoxy.

Waals interactions with the vicinal OR group of the nitrone and the 1,6-anhydro bridge of **7** are avoided.

Reactions of nitrones **11** and **12** with **7** occur with double asymmetric induction through "matched" interactions.

Scheme 2[a]



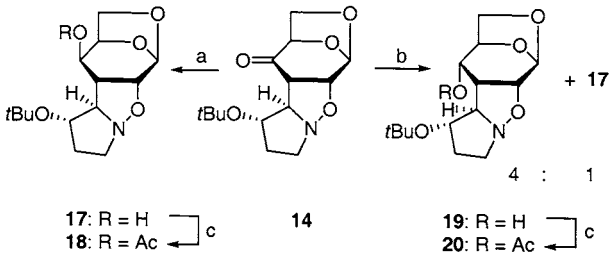
[a] Reaction conditions: (a) 2 equiv of (*rac*)-**15**, toluene, rt, 2.5 h.

The high facial preference shown allowed partial kinetic resolution[19] of the cis-disubstituted racemic nitrone **15**.[20]

Reaction of isolevoglucosenone (**7**) with 2 equiv of racemic nitrone **15** gave a major *exo*-anti adduct **16**, whose structure has been determined by X-ray analysis, in 32% yield, and 50% of enantioenriched (3*S*,4*R*)-nitrone **15** was recovered (54% ee).[21,22] The presence of a minor adduct, which has not been fully characterized yet, was visible in the ^{1}H NMR spectrum of the crude reaction mixture.

Cycloadducts **13**, **14**, and **16** can be readily converted into imino-*C*-disaccharides. For example, stereoselective reduction of the carbonyl moiety at C-4 of **14** using either DIBAL-H at low temperature or $NaBH_4$ at room-temperature opens the way to D-gulo and D-allo imino-*C*-disaccharides, respectively (Scheme 3). When adduct **14** was reacted with

Scheme 3[a]



[a] Reaction conditions: (a) DIBAL-H (1.5 equiv), CH_2Cl_2, −78 °C, 4 h, 74%. (b) $NaBH_4$ (3.5 equiv), EtOH, rt, 2.5 h, 90%. (c) Ac_2O, py, rt, 5.5 h and 75% yield for **18**, 16 h and 90% yield for **20**.

1.5 equiv of DIBAL-H at −78 °C, the sole *endo* alcohol **17** was formed. Reaction of **14** with an excess of $NaBH_4$ at

(16) For more recent syntheses of **7**, see: (a) Witczak, Z. J.; Chen, H.; Kaplon, P. *Tetrahedron*: *Asymmetry* **2000**, *11*, 519−532. (b) Kadota, K.; ElAzab, A. S.; Taniguchi, T.; Ogasawara, K. *Synthesis* **2000**, 1372−1374. (c) Witczak, Z. J.; Kaplon, P.; Kolodziej, M. *J. Carbohydr. Chem.* **2002**, *21*, 143−148.

(17) Cicchi, S.; Höld, I.; Brandi, A. *J. Org. Chem.* **1993**, *58*, 5274−5275.

(18) Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743−4748.

(19) For an account on kinetic resolutions by means of cycloaddition reactions, see: Cardona, F.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **2001**, 2999−3011.

(20) Goti, A.; Cicchi, S.; Cacciarini, M.; Cardona, F.; Fedi, V.; Brandi, A. *Eur. J. Org. Chem.* **2000**, 3633−3645.

(21) By means of cycloadditions to triacetyl-D-glucal, (3*S*,4*R*)-nitrone **15** could be recovered with 37% ee: Cardona, F.; Valenza, S.; Goti, A.; Brandi, A. *Eur. J. Org. Chem.* **1999**, 1319−1323.

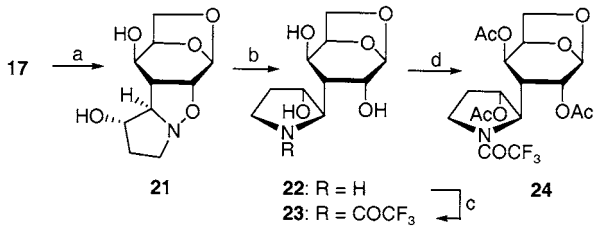
(22) Ee of the recovered nitrone was determined by ^{1}H NMR experiment with $Yb(hfc)_3$ as a chiral shift reagent: Cicchi, S.; Corsi, M.; Brandi, A.; Goti, A. *J. Org. Chem.* **2002**, *67*, 1678−1681.

room temperature, on the contrary, afforded a 4:1 mixture of **19** and **17** (with $LiAlH_4$ at −78 °C, a 1:1 mixture of the two alcohols was formed). The relative configurations of **17** and **19** were determined by analysis of ^1H NMR and two-dimensional COSY spectra of their acetates **18** and **20** and by X-ray analysis of **20**, which also confirms the stereochemistry assigned to adduct **14** (Scheme 3).

The dioxolane ring opening of the anhydropyranose moiety was troublesome. No bridge opening occurred upon treatment of **17** with anhydrous methanol saturated with HCl (65 °C, 15 h) or with a 2-fold excess of *p*TsOH in MeOH at reflux temperature for 3.5 h. The methodology proposed by Witczak and co-workers[23] for the hydrolysis of anhydropyranoses, already used by Vogel et al.,[8b] was successfully applied.

After deprotection of the *t*Bu group of **17** with *p*TsOH, N−O bond cleavage was readily achieved by hydrogenation of crude diol **21** over $Pd(OH)_2/C$ (Scheme 4). Protection of

Scheme 4[a]



[a] Reaction conditions: (a) *p*TsOH, reflux, 3.5 h. (b) $Pd(OH)_2/C$, H_2, MeOH, overnight. (c) TFFA, TFA, overnight, then MeOH, aqueous NH_3, 10 min. (d) Ac_2O, py, overnight, 29% yield from **17**.

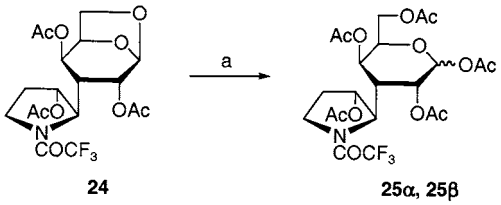
the amine moiety of crude **22** as a trifluoroacetamide was carried out by treatment with $(CF_3CO)_2O$ and trifluoroacetic acid, followed by methanolysis in the presence of catalytic ammonia,[24] which led to **23**. Peracetylation of crude **23** under standard conditions (Ac_2O, pyridine) gave triacetate **24**, obtained after FCC in 29% yield over four steps starting from **17** (Scheme 4).

Finally, acetolysis of **24** with acetic anhydride and trifluoroacetic acid afforded **25** in 93% yield as a 1.4:1

(23) Witczak, Z. J.; Chhabra, R.; Chen, H.; Xie, X.-Q. *Carbohydr. Res.* **1997**, *301*, 167−175.

(24) Chen, X.-Y.; Link, T. M.; Schramm, V. L. *J. Am. Chem. Soc.* **1996**, *118*, 3067−3068.

Scheme 5[a]



[a] Reaction conditions: (a) TFA, Ac_2O, 24 h, 93%.

mixture of the β- and α-isomers, which could be partially separated by flash column chromatography (Scheme 5). It should be noted that acetolysis on **17** or on the diacetate of **21** did not succeed, showing that assistance of the acetoxy group at C-2 is needed.

Compound **25** is an immediate precursor of a new directly linked (1→3)-imino-*C*-disaccharide in the D-gulo series.

In conclusion, we have presented the potential of the present approach for the synthesis of a broad new class of directly linked (1→3)-imino-*C*-disaccharides, by means of cycloadditions of polyhydroxylated cyclic nitrones to isolevoglucosenone. Work is underway in our laboratories to widen the scope of this approach for a general synthesis of imino-*C*-disaccharides and to evaluate their efficiency as glycosidase inhibitors.

Acknowledgment. We thank Dr. Cristina Faggi for her determinant contribution on X-ray crystal structure determination. This work was supported by a research grant from the University of Florence, Italy (Progetto Giovani Ricercatori 2002) and by the Ministry of Instruction, University and Research (MIUR, Cofin 2002), Italy.

Supporting Information Available: Experimental procedures for all new compounds. Full characterization for compounds **13**, **14**, **16**, **18**, **20**, and **25**; ^1H NMR, ^{13}C NMR, MS, and IR spectra for compounds **17** and **19**; ^1H NMR and ^{13}C NMR spectra for compound **24**; X-ray data for compounds **16** and **20** in CIF format; and Copies of ^1H and ^{13}C NMR spectra of compounds **13**, **14**, **16**−**20**, **24**, **25**α, and **25**β. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0342507