JOC*Note*

Synthesis and Intramolecular Nitrile Oxide Cycloaddition of 3,5′-Ether-Linked Pseudooligosaccharide Derivatives: An Approach to Chiral Macrooxacycles

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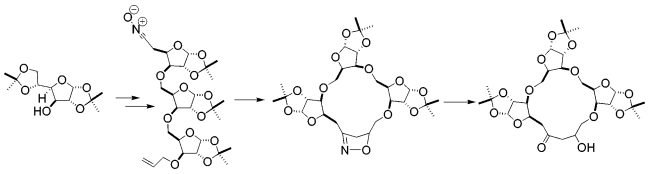
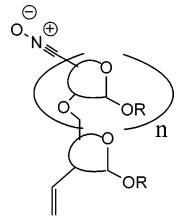


3,5′-Ether-linked pseudooligopentose derivatives were synthesized for the first time from readily available carbohydrate precursors. The 1,2-isopropylidene-protected ether-linked oligopentoses are potentially important as precursors of novel RNA analogues. Intramolecular cycloaddition of the nitrile oxides prepared from these derivatives led to the diastereoselective formation of chiral isoxazolines fused to 10−16-membered oxacycles. The stereochemistry of some of these isoxazolines was established by X-ray diffraction and NOESY analysis.

Intramolecular 1,3-dipolar nitrile oxide cycloaddition is one of the most important methods for the synthesis of cyclic compounds.[1] The application of this and the related nitrone cycloaddition in *O*- and *N*-alkenylcarbohydrate derivatives is an emerging area devoted to the synthesis of a variety of enantiopure cyclic compounds including cyclic ethers and amines.[2] The synthesis of macrocyclic rings by the application of intramolecular nitrile oxide cycloaddition has been reported,[3] although the synthesis of medium-ring compounds has rarely been accomplished using this method.[3d,4] In general, the synthesis of medium rings by conventional cyclization methods is difficult, and only recently with the introduction of efficient ring-closing metathesis catalysts has the preparation of medium rings become a simpler task.[5] However, apart from their operational simplicity the nitrile oxide and the related nitrone cycloaddition reactions are more atom-economic, and the products are amenable to transformations that can lead to the introduction of extra functionalities. While chiral benzo-fused eight- to 12-membered medium-sized cyclic ethers fused to isoxazoline rings have been obtained by cycloaddition of nitrile oxides having 1,2-disubstituted phenyl rings as structural constraints,[6] a remaining challenge in this area is the utilization of a chiral nonaromatic alkene-bearing carbohydrate ring as a structural constraint. In this way, the nitrile oxide cycloaddition would provide macrocyclic compounds devoid of any benzo fusion and allow for the introduction of additional chiral centers present in the carbohydrate ring. An ether-linked pseudooligosaccharide **1** appeared to be an attractive scaffold for performing the aforementioned nitrile oxide cycloaddition, because the anomeric sites of the carbohydrate units in the resulting cycloadducts would be available for further elaborations including conjugation with other bioactive units such as peptides as well as conversion to nucleosides. Another important aspect of this reaction is that it might allow for the preparation of medium-sized rings from substrates of suitable sizes. Ether-linked pseudooligosaccharide derivatives have received little attention, and only a few 2,6′-, 3,6′-, and 6,6′-ether-linked dihexoses are known.[7] A 3,5′-ether-linked oligopentose molecule is of particular interest due to its close similarity to the nucleic acid backbone. We describe herein the synthesis of hitherto unreported 3,5′-ether-linked pseudooligopentose derivatives and their intramolecular nitrile oxide cycloaddition leading to the synthesis of isoxazolines fused to 10−16-membered oxacycles.



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The attempted synthesis of a 3,5′-linked pseudodisaccharide **4** by alkylation of commercially available 1,2:5,6-diisopropylideneglucofuranose (**3**) with the known mesyl derivative **2**[8] in the presence of NaH in THF or DMF was unsuccessful. The adoption of a reported[9] procedure for the synthesis of ethers involving extended heating of a mixture of **2** and **3** in aqueous NaOH in the presence of

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(1) (a) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1069. (b) Wade, P. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1111.

(2) (a) Gothelf, K. V.; Jorgensen, K. A. *Chem. Rev.* **1998**, *98*, 863. (b) Frederickson, M. *Tetrahedron* **1997**, *53*, 403. (c) Osborn, H. M. I.; Gemmell, N.; Harwood, L. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2419.

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(4) (a) Kozikowski, A. P.; Mugrage, B. B. *J. Chem. Soc., Chem. Commun.* **1988**, 198. (b) Rai, K. M. L.; Hassner, A. *Heterocycles* **1990**, *30*, 817. (c) Bode, J. W.; Carreira, E. M. *J. Org. Chem.* **2001**, *66*, 6410.

(5) (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

(6) Majumdar, S.; Mukhopadhyay, R.; Bhattacharjya, A. *Tetrahedron* **2000**, *56*, 8945.

(7) (a) Whistler, R. L.; Frorein, A. *J. Org. Chem.* **1961**, *26*, 3946. (b) Hodosi, G.; Kovác, P. *Carbohydr. Res.* **1998**, *308*, 63. (c) Vanbaelinghem, L.; Godé, P.; Goethals, G.; Martin, P.; Ronco, G.; Villa, P. *Carbohydr. Res.* **1998**, *311*, 89. (d) Haines, A. H. *Tetrahedron Lett.* **2004**, *45*, 835. (e) Haines, A. H. *Org. Biomol. Chem.* **2004**, *2*, 2353.

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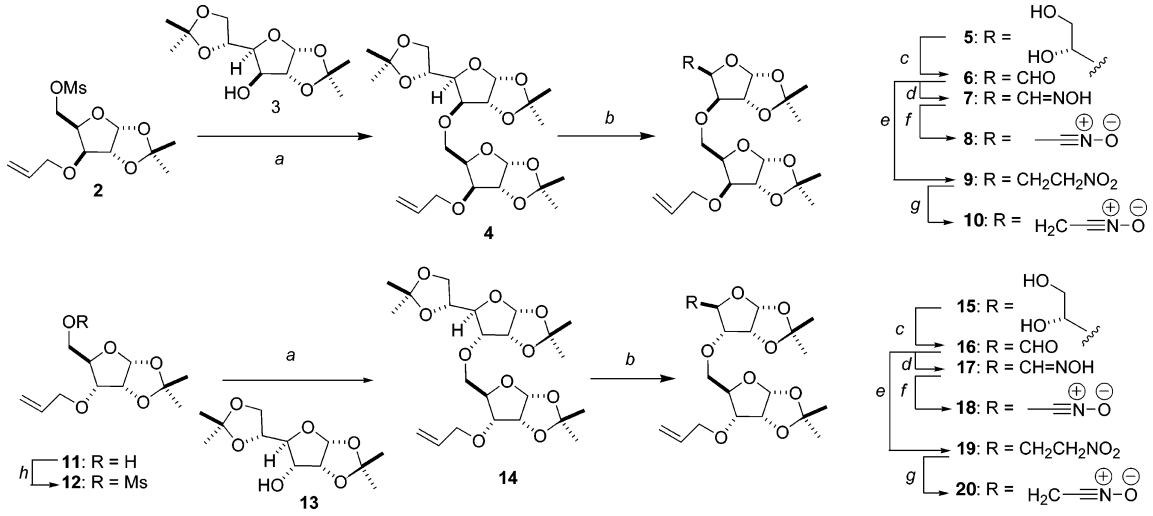
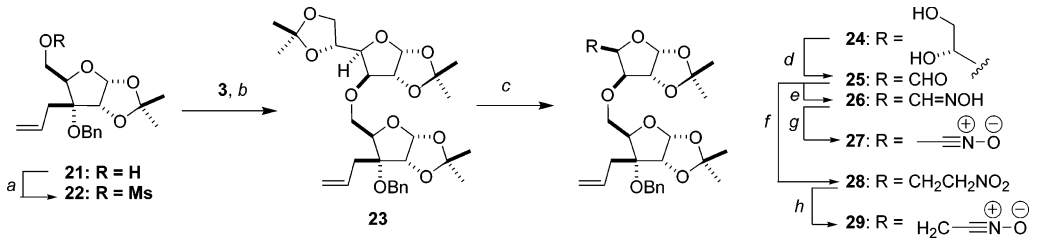
SCHEME 1. Synthesis of the Pseudodisaccharides 4 and 14 and Their Conversion to Nitrile Oxides[a]



[a] Reagents: (a) $(Bu)_4NBr$, 11% aq. NaOH, 70 °C, 70 h, 80% (**4**), 84% (**14**). (b) 50% aq. AcOH, 25 °C, 15 h, 98% (**5**), 97% (**15**). (c) $NaIO_4$, $MeOH-H_2O$, 25 °C, 2 h, 94% (**6**), 95% (**16**). (d) $NH_2OH{\cdot}HCl$, py, EtOH, reflux, 4 h, 88% (**7**), 80% (**17**). (e) i. $MeNO_2$, *i*-PrOH, KF, 25 °C, 24 h, ii. Ac_2O, DMAP, Et_2O, 0 °C, 2 h, iii. $NaBH_4$, EtOH, 25 °C, 6 h, 52% (**9**), 56% (**19**). (f) *N*-Chlorosuccinimide, DMAP, CH_2Cl_2, 25 °C, 48 h. (g) 4-Chlorophenylisocyanate, Et_3N, benzene, 25 °C, 48 h. (h) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 1 h, 0−25 °C, 90%.

SCHEME 2. Synthesis of 23 and Its Conversion to Nitrile Oxides[a]



[a] Reagents and conditions: (a) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 1 h, 0−25 °C, 97%. (b) $(Bu)_4NBr$, 11% aq. NaOH, 70 °C, 70 h, 93%. (c) 50% aq. AcOH, 25 °C, 15 h, 97%. (d) $NaIO_4$, $MeOH-H_2O$, 25 °C, 2 h, 98%. (e) $NH_2OH.HCl$, py, EtOH, reflux, 4 h, 90%. (f) i. $MeNO_2$, *i*-PrOH, KF, 25 °C, 24 h, ii. Ac_2O, DMAP, Et_2O, 0 °C, 2 h, iii. $NaBH_4$, EtOH, 25 °C, 6 h, 65%. (g) *N*-Chlorosuccinimide, DMAP, CH_2Cl_2, 25 °C, 48 h. (h) 4-Chlorophenylisocyanate, Et_3N, benzene, 25 °C, 48 h.

tetrabutylammonium bromide successfully led to the formation of the 3,5′-ether-linked pseudodisaccharide **4** in 80% yield (Scheme 1).[10] The structure of **4** was secured from NMR and mass spectral analyses. A sequence of reactions involving selective deprotection by treatment with 50% aqueous HOAc to **5**, vicinal diol cleavage with $NaIO_4$ to **6**, and subsequent oximation gave **7**. In a separate route, aldehyde **6** was converted to nitro compound **9** following a known protocol involving reaction with nitromethane, acetylation, and reduction with sodium borohydride without isolating or purifying the intermediates.[11] Similarly, the pseudodisaccharide derivative **14** was prepared from 3-*O*-allyl-1,2:5,6-diisopropylideneallofuranose (**13**)[12] and the known mesyl derivative **12**,[8] which was prepared from the known[8] alcohol **11** by mesylation with $MeSO_2Cl$ in the presence of triethylamine. Ether **14** was then converted to oxime **17** and nitro derivative **19** by the earlier mentioned methods. Pseudodisaccharide **23**, oxime **26**, and nitro compound **28** were prepared by the abovementioned methods from **3** and the known[8] 3-*C*-allyl ribose derivative **21** (Scheme 2).

Pseudotrisaccharide **32** was synthesized by coupling **3** with the mesyl derivative **31**, which was obtained by $NaBH_4$ reduction of aldehyde **6** → **30** followed by mesylation. Oxime **35** and nitro derivative **37** were prepared in the usual manner (Scheme 3).

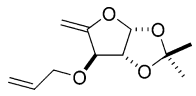
To our knowledge, the pseudooligosaccharide derivatives cited in the above schemes are the first examples of 3,5′-ether-linked species, and the method used for their synthesis constitutes an operationally simple alternative to existing protocols.[7]

Oximes **7**, **17**, **26**, and **35** were converted to their respective nitrile oxides **8**, **18**, **27**, and **36** by treatment with *N*-chlorosuccinimide and DMAP,[13] while nitro compounds **9**, **19**, **28**, and **37** furnished nitrile oxides **10**, **20**,

(8) Tripathi, S.; Singha, K.; Achari, B.; Mandal, S. B. *Tetrahedron* **2004**, *60*, 4959; corrigendum, *Tetrahedron* **2005**, *61*, 6154.

(9) Tranmer, G. K.; Tam, W. *J. Org. Chem.* **2001**, *66*, 5113.

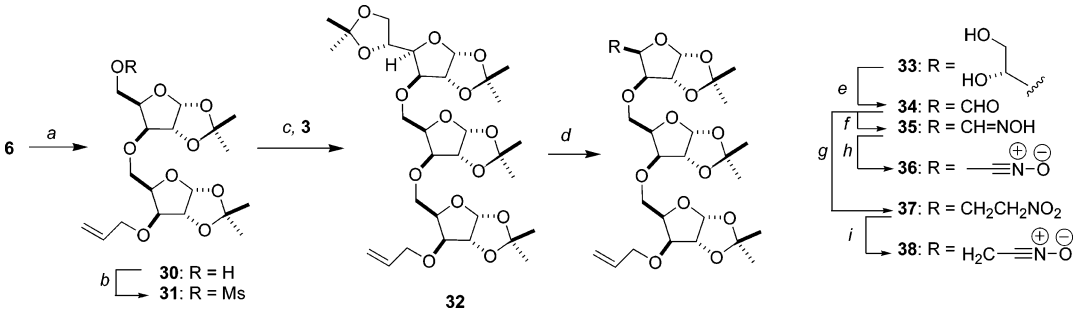
(10) A minor olefinic product derived by the elimination of MsOH from the mesylate **2** was obtained in this reaction. The ^1H NMR spectrum of the compound suggested the structure shown below. Scaling up of the alkylation resulted in the increased formation of this side product. Similar olefinic minor products were also encountered in the other alkylation reactions described in this work.



(11) Kozikowski, A. P.; Li, C.-S. *J. Org. Chem.* **1985**, *50*, 778.

(12) Baker, D. C.; Horton, D.; Tindal, C. G., Jr. *Carbohydr. Res.* **1972**, *24*, 192.

SCHEME 3. Synthesis of the Pseudotrisaccharide 32 and Its Conversion to Nitrile Oxides[a]



[a] Reagents and conditions: (a) $NaBH_4$, MeOH, 25 °C, 6 h, 89%. (b) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 1 h, 0−25 °C, 93%. (c) $(Bu)_4NBr$, 11% aq. NaOH, 70 °C, 70 h, 83%. (d) 50% aq. AcOH, 25 °C, 15 h, 99%. (e) $NaIO_4$, MeOH−H_2O, 25 °C, 2 h, 98%. (f) NH_2OH·HCl, py, EtOH, reflux, 4 h, 71%. (g) i. $MeNO_2$, *i*-PrOH, KF, 25 °C, 24 h, ii. Ac_2O, DMAP, Et_2O, 0 °C, 2 h, iii. $NaBH_4$, EtOH, 25 °C, 6 h, 52%. (h) *N*-Chlorosuccinimide, DMAP, CH_2Cl_2, 25 °C, 48 h. (i) 4-Chlorophenylisocyanate, Et_3N, benzene, 25 °C, 48 h.

29, and **38** by reaction with 4-chlorophenylisocyanate.[14] The concomitant cycloaddition of these nitrile oxides occurs in situ; the results of these cycloadditions are presented in Table 1.

As seen from Table 1, all the nitrile oxides except **18** and **27** (entries 3 and 5) underwent cycloaddition giving rise to the oxacycle-fused isoxazolines **39**−**44**. Intractable mixtures were obtained from the reactions of **18** and **27**. No nitrile oxide dimers or dimeric isoxazolines could be isolated from these reactions. The majority of the products were bridged isoxazolines with the exception of **42**, which was a fused isoxazoline. The reasons for the failure of **18** and **27** to undergo cycloaddition are not known, although it is possible that the unfavorable steric and transannular interaction in the medium-ring transition states prevented the reaction. The gross structures of these isoxazolines were easily ascertained by NMR and mass spectral analyses. The presence of the bridge $-CH_2-$ in a bridged isoxazoline was established by the appearance of two sets of doublets with a large J_{gem} (∼16 Hz) in the ^{1}H NMR spectrum as well as a high-field methylene carbon signal in the ^{13}C NMR spectrum. The yields (50−87%) observed in these cycloadditions are quite impressive considering the sizes of the oxacycles formed, which ranged between 10 and 16. The diastereoselectivity and the regioselectivity of these cycloadditions warrant special mention because a single product was obtained in each of the successful reactions. The stereochemistry of the newly formed chiral center in **39** was established by X-ray diffraction analysis (Figure 1),[15] whereas in **40**, **41**, and **42**, it was established by NOESY analysis. The NOESY spectrum of **39** did not reveal any NOE correlation of the bridge methylene protons or of the newly formed chiral center with any existing chiral center. The NOESY spectrum of the higher homologue **40** was very similar to that of **39** and did not exhibit any NOE of the proton attached to the newly formed chiral center with those of the existing chiral centers. It was apparent that **39** and **40** should have closely similar structures, and hence the stereochemistry of the newly formed centers in these compounds is expected to be identical. The assignment also appeared logical from the viewpoint of the faciality of approach of the reacting dipole and the dipolarophile in the nitrile oxide **10**, which should be similar to that observed in its lower homologue **8**. The observation of the relevant NOE correlations shown in Figure 2 (in the Supporting Information) led to the assigned stereochemistry in **41** and **42**. The stereochemistry of **43** and **44** could not be established due to their poorly resolved ^{1}H NMR spectra and the failure to obtain suitable crystals for X-ray analysis. However, their gross structures could be unambiguously determined by the appearance of the signals due to the bridge $-CH_2-$ with high geminal coupling constants in the ^{1}H NMR spectra as well as by the adequate ^{13}C NMR and mass spectral data.

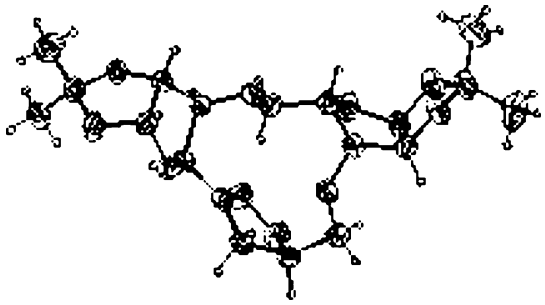


FIGURE 1. ORTEP view of **39**.

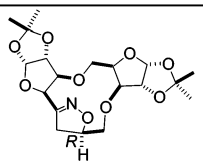
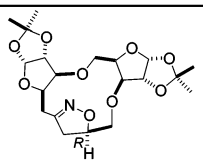
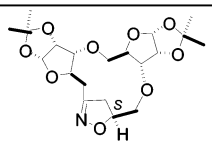
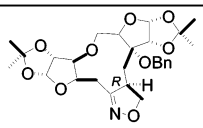
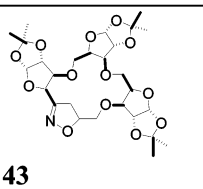
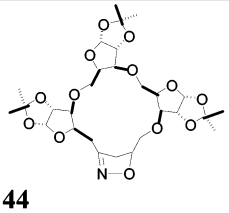
Nitrile oxides **8**, **10**, **20**, and **29** (entries 1, 2, 4, and 6) gave rise to products that contain medium-sized (10−12-membered) oxacycles fused to isoxazoline rings.

(13) Liu, K.-C.; Shelton, B. R.; Howe, R. K. *J. Org. Chem.* **1980**, *45*, 3916.

(14) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339.

(15) Crystal data for **39** $C_{19}H_{27}NO_9$ $M = 413.42$, crystal dimensions $0.36 \times 0.18 \times 0.12$ mm^3, orthorhombic, space group $P2(1)2(1)2(1)$, $a = 6.8229(8)$, $b = 15.4730(17)$, $c = 18.734(2)$ Å, $V = 1977.8(4)$ Å^3, $Z = 4$; $\rho_{calcd} = 1.388$ g cm^{-3}, μ (Mo Kα) = 0.111 mm^{-1}, $2\theta_{max} = 50.0°$, 9953 reflections collected, 3443 unique, 2897 observed ($I > 2\sigma(I)$) reflections, 226 refined parameters, R value 0.0456, $wR2 = 0.0755$ (all data $R = 0.0586$, $wR2 = 0.0789$), $S = 1.097$, maximum and minimum residual electron densities 0.127 and −0.128 Å^{-3}. X-ray data intensity was collected on a SMART APEX CCD diffractometer with omega and phi scan mode, $\lambda_{MoK\alpha} = 0.71073$ Å at $T = 293(2)$ K. All the data were corrected for Lorentzian, polarization, and absorption effects using SAINT and SADABS programs. SHELX-97 (Sheldrick, G. M. *SHELX-97: Program for Crystal Structure Solution and Refinement*; University of Göttingen: Göttingen, Germany, 1997) was used for structure solution and full-matrix least squares refinement on F^2. Hydrogen atoms were located in the difference Fourier map but were refined using riding model option in the least-squares refinement. Crystallographic data (excluding structure factors) for **39** reported in this note have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 258842. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: (+44)-1223-336-033; or deposit@ccdc.cam.ac.uk).

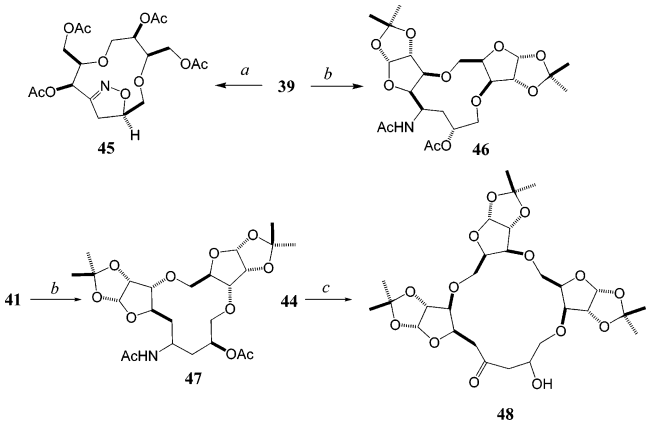
TABLE 1. Intramolecular Nitrile Oxide Cycloaddition of Pseudooligosaccharide Derivatives[a]

Entry	Nitrile oxide precursor	Nitrile oxide	Product	Yield (%)[b]
1	**7**	**8**	 **39**	50
2	**9**	**10**	 **40**	52
3	**17**	**18**	c	
4	**19**	**20**	 **41**	87
5	**26**	**27**	c	
6	**28**	**29**	 **42**	52
7	**35**	**36**	 **43**	50
8	**37**	**38**	 **44**	82

[a] Nitrile oxides were generated from the oximes by treatment with *N*-chlorosuccinimide at 25 °C and DMAP or from the nitro compounds by treatment with 4-chlorophenylisocyanate and triethylamine at 25 °C. The cycloadditions took place in situ. [b] Chromatographically isolated yields. [c] Intractable mixtures were obtained in these reactions.

The formation of "fused" isoxazoline **42** from **29** reflected the conformational intricacies associated with these medium rings. The presence of the *O*-benzyl group in one of the furanoside rings in the nitrile oxide **29** probably contributed to enhanced transannular and steric interactions in the transition state involved in the formation of the alternative "bridged" bicyclic ring. Nitrile oxides **36** and **38** (entries 7 and 8) represent two particularly interesting substrates incorporating 3,5′-ether-linked

SCHEME 4. Degradation of 39, 41, and 44[a]



[a] Reagents: (a) i. 4% aq. H_2SO_4−CH_3CN, 25 °C, 48 h, ii. $NaIO_4$, MeOH−H_2O, 25 °C, 2 h, iii. $NaBH_4$, EtOH, 0−25 °C, 6 h, iv. Ac_2O, Et_3N, DMAP, EtOAc, 25 °C, 6 h, 14%. (b) i. $LiAlH_4$, Et_2O, 25 °C, 24 h, ii. Ac_2O, py, 25 °C, 12 h, 50% (**46**), 67% (**47**). (c) Raney-Ni, H_2, MeOH−H_2O (10:1), HOAc, 25 °C, 36 h, 75%.

pseudotrisaccharide scaffolds having multiple substitutions and three ether linkages in the acyclic backbone. The resulting cycloadducts **43** and **44** are characterized by the presence of polyether macrocycles of ring sizes 15 and 16.

The advantage of the isopropylidene-protected furanoside ring in the above cycloadducts was demonstrated by the facile degradation of **39** to **45** in 14% overall yield via a well-established sequence of reactions involving removal of the isopropylidene groups, vicinal diol cleavage by $NaIO_4$, reduction of the resulting aldehyde by $NaBH_4$, and acetylation (Scheme 4).[16] Alternatively, the isoxazoline rings in **39** and **41** were cleaved by $LiAlH_4$, and the resulting amino alcohols were acetylated to furnish the furanoside-fused oxacycles **46** and **47** in 50 and 67% overall yields, respectively (Scheme 4). The reduction was found to be stereoselective in both cases, although the stereochemistry of the carbon atoms bearing the acetamido groups could not be established. In a different approach, reductive cleavage of isoxazoline **44** by hydrogenation in the presence of Raney nickel and acetic acid afforded the keto alcohol **48** in 75% yield (Scheme 4).[11]

In conclusion, the work in this note presents a convenient method for the synthesis of 3,5′-ether-linked pseudooligosaccharides and a novel approach to chiral macrooxacycles by the application of nitrile oxide cycloaddition. These 3,5′-ether-linked pseudooligosaccharides are potentially important for the synthesis of RNA analogues, and work toward this goal will be reported in due course.

Acknowledgment. J.S. is grateful to CSIR, India, for the award of a Senior Research Fellowship. Thanks are due to Mr. A. Banerjee, Mr. K. Sarkar, and Mr. S. Chowdhury for spectral analyses.

Supporting Information Available: Experimental procedure, NMR spectra, and CIF file. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050689W

(16) Bhattacharjee, A.; Datta, S.; Chattopadhyay, P.; Ghoshal, N.; Kundu, A. P.; Pal, A.; Mukhopadhyay, R.; Chowdhury, S.; Bhattacharjya, A.; Patra, A. *Tetrahedron* **2003**, *59*, 4623.