Diastereoselective Cycloadditions of Nitroalkenes as an Approach to the Assembly of Bicyclic Nitrogen Heterocycles†

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Received September 22, 1998

A three-component coupling for the rapid assembly of nitrogenated bicycles has been developed that employs the sequential cycloaddition of nitroalkenes as 4π components and both an electron-rich vinyl ether and electron-withdrawing alkenes. Given the distinct electronic character of nitroalkenes and the intermediate nitronates, the coupling represents an atom-economy strategy without side products resulting from competitive reactions. Either with a racemic nitroalkene or an enantiopure nitroalkenyl sugar, these processes were regiospecific leading to the formation of bicyclic nitrosoacetals with high facial diastereoselectivity. The stereochemistry of the cycloadducts was assigned by NMR spectroscopic techniques, and those of **2** and **15** were corroborated by X-ray crystallographic analysis. The unmasking of the nitrosoacetal moiety under mild conditions represents a homologation route for higher aldehydo sugars.

Introduction and Background

Cycloaddition reactions represent cornerstone processes in organic chemistry by virtue not only of the number of bonds involved but also for the controlled installation of multiple stereogenic centers.[1] These reactions are therefore a favorite methodology that vastly increases molecular complexity, thereby finding wide application for the synthesis of naturally occurring and/or biologically active compounds.[2] One of the most useful reactions in this field is the tandem cycloaddition of nitroalkenes leading to highly valuable polycyclic pyrrolidine alkaloids.[3,4] In particular, Denmark and his associates have concentrated on Lewis acid-catalyzed inter-[4 + 2]/intra[3 + 2] cycloadditions of nitroalkenes with chiral vinyl ethers for the construction of polycyclic nitrogen bases.[3] In agreement with a typical inverse electron demand cycloaddition, the initial Diels−Alder reaction displays a preference for the kinetically favored endo adduct and the subsequent dipolar process follows in situ in the exo orientation, thereby ensuring a controlled stereochemical outcome. Recently, Dutch authors have showed that tandem nitroalkene cycloadditions can be accelerated under high pressure either in solution[5] or on the solid phase using a resin-bound acrylate,[6] which obviates the need for both a Lewis acid catalyst and a large excess of vinyl ether.

From a stereochemical viewpoint the construction of a molecular framework by tandem cycloadditions is a challenging task owing to the possible limiting combinations of the two reacting partners. Thus, the enol ether can adopt either s-cis or s-trans geometry[7] attacking to the re or si face of the heterodiene (respect to the nitroalkene β carbon atom) in an endo or exo approach. At first glance, a high level of stereoselection is not expected unless a homochiral auxiliary allows control of stereocenters. Chiral enol ethers[3] and nitroalkenes[8,9] have been utilized in asymmetric versions of the tandem nitroalkene cycloaddition. In a previous work, we have described a highly stereoselective intermolecular tandem cycloaddition starting from a carbohydrate-based nitroalkene that is readily available in enantiopure form (Scheme 1).[9] With the Diels−Alder reaction, the stereochemistry for the rest of the molecule was set in the first

† Dedicated to the memory of Vlado Prelog (1906−1998), one of the greatest chemists of this century.

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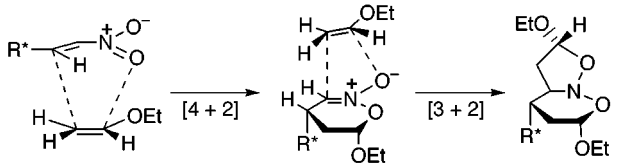
10.1021/jo981921j CCC: $18.00
Published on Web 02/05/1999

Scheme 1. Tandem Cycloaddition of a Chiral Nitroalkene with Ethyl Vinyl Ether



R* = D-*galacto*-$(CHOAc)_4CH_2OAc$

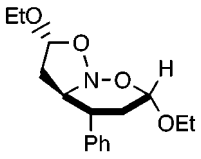
reaction. The result is an economical synthesis that avoids costly and wasteful resolution steps.

In this stage of involvement with vinyl ethers, it seemed likely that opportunity for variation in the system undergoing cyclization could be achieved by combining in situ nitroalkenes with electron-rich and electron-withdrawing alkenes, provided that these latter compounds do not react each other. A generalizable part of this chemistry was also the finding that the starting nitroalkene did not react at all with an electron-poor alkene, as it would otherwise be expected for an inverse demand cycloaddition. A pleasing outcome in this regard was the development of a three-component reaction since the nitroalkene reacts exclusively with an enol ether while the in situ formed nitronate will be trapped selectively by the electron-withdrawing alkene.[10] In an independent work Scheeren and co-workers have reached the same conclusion in the reaction of nonactivated nitroalkenes with ethyl vinyl ether and methyl acrylate.[5] The overall process also benefits from the fact that nitronates react faster with electron-withdrawing alkenes than with electron-rich alkenes,[8,11] thus avoiding competing side reactions. In this context, it should also be mentioned a recent contribution by Italian authors who have devised a three-component reaction involving an aldehyde, an activated primary nitroalkane, and a chlorodialkyl vinylsilane to afford a bicyclic nitrosoacetal with high selectivity.[12] Accordingly, we felt it would be useful to investigate our preliminary results in a broader study.

Results and Discussion

Cycloaddition Reactions: Scope and Stereochemistry. To delineate the scope of the fully intermolecular tandem process, we performed the reaction of *β*-nitrostyrene (**1**) with ethyl vinyl ether (EVE) in ethanolic solution at room temperature. As expected the nonchiral process afforded the tandem cycloadduct **2**, which could be isolated in crystalline form and its structure was determined by single-crystal X-ray diffraction (see Supporting Information).[13]

The stereostructure reveals the preferred conformation of the bicyclic arrangement in the solid state. The five-membered ring adopts an envelope conformation with a carbon atom lying 0.526 Å from the plane, whereas the six-membered 1,2-oxazine ring exhibits a twist-boat conformation. Likewise, the substituents of the bicyclic system (phenyl and ethoxy groups) display a cis relative disposition. In previous studies of tandem nitroalkene cycloadditions, it has been demonstrated that the major isomer displays an α-oriented alkoxy group arising from an endo transition state (TS) for the [4 + 2] cycloaddition.[9,14] Such a pseudoaxial configuration suggests the existence of an *anomeric effect*, namely a stabilizing interaction between a nonbonding electron pair on oxygen and the low-energy antibonding orbital of a contiguous C-heteroatom bond, which is commonly found in pyranoses and in tetrahydropyranyl acetals in general.[15] The most direct evidence for this interaction is the systematic variation in the pattern of bond lengths at the carbon center of such systems when the electronegativity of the heteroatom is changed.[15,16] This interaction explains why the two C−O bonds at the six-membered ring of **2** differ in length, with the bond to the axial oxygen the longer since only this C−O bond is antiperiplanar to a lone pair on the other oxygen atom. For compound **2**, bond lengths O_{ring}−C and C−OEt are 1.416 and 1.394 Å, respectively. Furthermore, the pseudoaxial disposition manifests itself through NMR data in solution: H-6 exhibits coupling constants of 7.6 and 6.8 Hz with its adjacent protons H-5 and H-5′.



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As previously noted, the reacting conformation of the enol in the orientation of approach to the nitroalkene may also play an important role. In the case of small enol ethers the energetic barrier between s-cis and s-trans conformers is too low and there is no preference for one of them.[7] Nevertheless, a recent finding by Houk and his associates should be pointed out. They have demonstrated that a conformational switch occurs during the course of reaction. Thus, the conformations of vinyl ethers in ground states change from a s-cis to a s-trans conformation in the transition structures, a fact primarily attributed to electrostatic effects and, to a lesser extent, steric effects.[7c]

Initially we did explore the reactions of **1** with EVE in the presence of an electron-poor alkene. Although the combination of reaction partners can lead to a high

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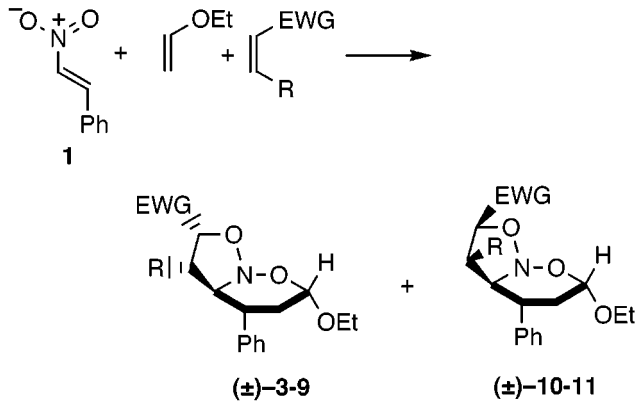
(15) For recent and excellent overviews, see: (a) *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; American Chemical Society: Washington, DC, 1993. (b) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press: Boca Raton, FL, 1995.

(16) A certain criticism of the relationship between crystal structure data and stereoelectronic effects persists, based on the following arguments: (a) crystal packing forces and dipolar interactions are dominant in the solid phase; (b) intermolecular interactions are usually neglected in the study of stereoelectronic effects in solution; (c) molecular structures and conformations may differ not only between solution and solid state but also between different crystal forms. See: Thatcher, G. R. J. in ref 15a, Chapter 2 and references therein.

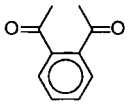
Scheme 2. A Three-Component Reaction of β-Nitrostyrene (1) with Electron-Rich and Electron-Poor Alkenes



number of diastereomeric products, it is interesting to note that we have been able to detect only one or two (TLC analysis and 400-MHz NMR monitoring). As with the structurally similar nitrosoacetal **2**, the above-mentioned transformations were regiospecific and proceeded with a high stereoselectivity. Still, they required the presence of large excesses of both alkenes and yields were moderate owing to the partial conversion of the starting nitroalkene. The reaction of **1** with EVE plus methyl acrylate afforded a mixture of two cycloadducts (**3** and **10**), chromatographic separation of which posed no problem, and they could further be isolated in crystalline form in 35 and 8% yield, respectively. Two tandem cycloadducts (**5** and **11**) were also detected and isolated as crystalline materials (50 and 6%, respectively) when **1** was reacted with EVE and acrylonitrile. In the reaction with dimethyl maleate only one cycloadduct (**4**) was isolated in 30% yield after chromatographic separation of the remaining nitroalkene. Likewise, only one cycloadduct was isolated in the tandem reactions with maleic anhydride, 1,4-benzoquinone, and 1,4-naphthoquinone (**6**, **8**, and **9**, respectively). Remarkably, we were able to detect two cycloadducts when the electron-withdrawing alkene was *N*-phenylmaleimide, but all attempts to isolate the minor product failed. These results are depicted in Scheme 2 and Table 1.

Asymmetric Reactions. The ever-increasing need for absolute stereochemical control in the construction of organic molecules has resulted in a series of strategies to accomplish effective asymmetric synthesis. In general, the formation of asymmetric centers can be obtained from prochiral starting molecules by either face-selective reactions (stereoheterotopic facial addition) or group-selective reactions (stereoheterotopic ligand substitution).[17] Stereoselective cycloadditions can be achieved by using dienophiles or 1,3-dienes, appropriately attached to suitable chiral auxiliaries of the chiral pool or prepared for this purpose.[1,18] The steering propensity of the chiral auxiliary derives from repulsive steric interactions between the auxiliary in the substrate and the attacking

Table 1. Tandem Adducts Obtained by Cycloaddition of 1 with EVE and Electron-Poor Alkenes

EWG	R	major isomer (%)[a]	minor isomer (%)[a]
COOMe	H	**3** (35)	**10** (8)
COOMe	COOMe	**4** (30)	
CN	H	**5** (50)	**11** (6)
—CO—O—CO—		**6** (30)	
—CO—N(Ph)—CO—		**7** (59)	—[b]
—CO—CH=CH—CO—		**8** (40)	
		**9** (28)	

[a]Yields refer to isolated crystalline materials. [b]Not isolated.

reaction partner,[19] thereby altering significantly the energetics of the competing diastereomeric transition structures of these stereodivergent processes.

As chiral auxiliary we chose an optically active nitroalkenyl sugar (**12**), easily generated from D-galactose.[20] Indeed, this auxiliary, which operate both through steric and conformational control, turned out to be a highly effective chiral inductor in the stereocontrolled three-component coupling.[10] The gratifying results obtained in the asymmetric version of this tandem process do illustrate anew the benefit of a vicinal chiral tether on the diastereoselection. Reactions were also carried out at room temperature in ethanol and required several days to give complete conversion of **12** to the tandem cycloadducts. Attempts to catalyze cycloadditions of nitroalkene **12** by Lewis acids were unsuccessful, presumably due to the competing coordination with the acetate protecting groups. Inspection of crude mixtures by ^{1}H NMR at 400 MHz revealed that addition took place regiospecifically, showing a marked facial diastereoselectivity as well since only two diastereomers were detected. Chromatographic purification afforded the corresponding adducts **13**−**18** as major isomers, which were further obtained in crystalline form in fairly good yields, as diastereomerically pure samples (Scheme 3, Table 2). Only one diastereoisomer could be isolated in tandem reactions either with dimethyl maleate or methyl vinyl ketone (adducts **14** and **16**, respectively). The corresponding reaction with methyl acrylate produced two adducts (**13** and **19**), separable by fractional crystallization, while the tandem adducts **15** and **20**, formed during the coupling with acrylonitrile, were isolated by chromatography. The reaction with *N*-phenylmaleimide proceeded with a lower selectivity, and the corresponding adducts (**17** and **21**) were isolated in 35 and 25% yields, respectively after purification by fractional crystallization. However, only one cycloadduct (**18**) could be detected in the reaction with 1,4-naphthoquinone, which was further isolated in 50% yield.

The structure of major isomers **13**−**18** was assumed on the basis of similar spectroscopic data to those of a

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Scheme 3. Chiral Nitrosoacetals Obtained from Nitroalkene 12 by a Multicomponent Reaction

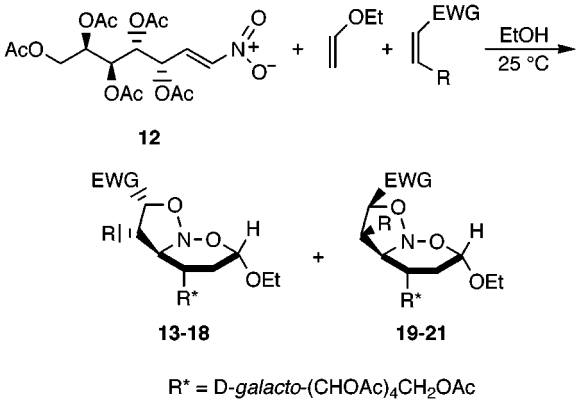
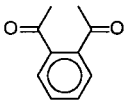


Table 2. Chiral Adducts Obtained in the Cycloaddition of 12 with EVE and Different Electron-Withdrawing Alkenes

EWG	R	major isomer (%)[a]	minor isomer (%)[a]
COOMe	H	**13** (75)	**19** (4)
COOMe	COOMe	**14** (50)	—[b]
CN	H	**15** (60)	**20** (10)
COMe	H	**16** (70)	—[b]
—CO—N(Ph)—CO—		**17** (35)	**21** (25)
		**18** (50)	

[a]Isolated yields of crystalline materials. [b]Not isolated.

chiral bicyclic system whose stereochemistry was determined by single-crystal X-ray diffraction.[9] These crystalline solids display in their ^{1}H NMR spectra the resonances of the two anomeric[21] protons which are significantly deshielded in the range of 4.7−5.0 ppm, and likewise the resonances for such anomeric carbons exhibit a strong nuclear deshielding characteristic of carbon atoms directly attached to two oxygen atoms.

The relative configurations of the anomeric carbons could be determined by analysis of the splitting pattern of their protons along with the information provided by the values of coupling constants. In the cycloaddition of **12** with EVE and methyl vinyl ketone leading to the nitrosoacetal **16**, the anomeric proton (H-2) located at the five-membered ring is observed as a doublet of doublets with couplings of 9.8 and 4.6 Hz with the vicinal protons H-3 and H-3′, respectively; the anomeric proton at the six-membered ring (H-6) appears as a triplet with a coupling constant of 7.0 Hz with its adjacent protons H-5

(21) In relation with bicyclic nitrosoacetals, the terms anomeric and pseudoanomeric have been utilized in the literature and may engender a certain controversy. We prefer to unify this terminology, and according to the recent IUPAC recommendations on stereochemistry (Moss, G. P. *Pure Appl. Chem.* **1996**, *68*, 2193−2222), such positions may be defined as anomeric. Likewise, the relative stereodescriptors α and β are also utilized by Chemical Abstracts Service to describe the configuration of a cyclic molecule (including polycyclic systems as well) with several stereogenic centers whereby the α side of the reference plane is the side on which the substituent with CIP priority lies at the lowest numbered stereogenic centre. The other side is β.

Scheme 4

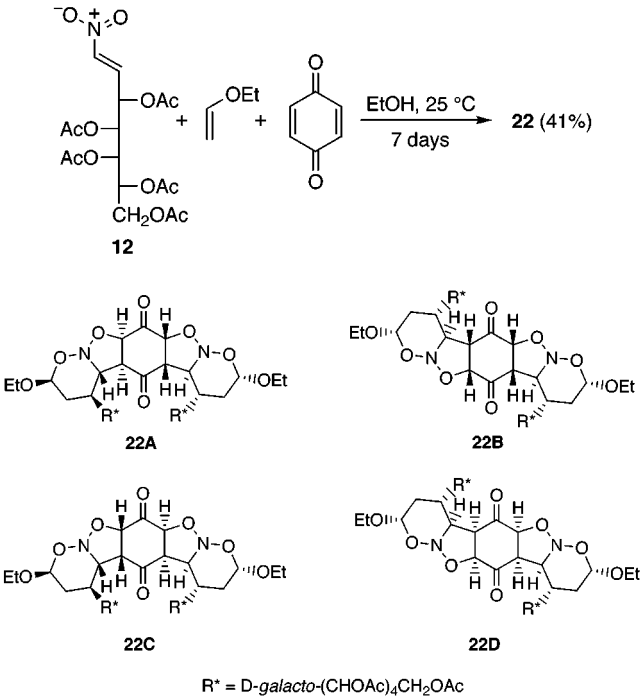


Figure 1. Possible structures **22A-22D** proposed for the tandem product in the reaction of **12** with EVE and 1,4-benzoquinone.

and H-5′. It is therefore interesting that the coupling pattern of such protons in the nitrosoacetals **13**−**18** displays the same behavior, with the exception of product **14**, for which the anomeric proton H-2 should be observed as a doublet. The analysis of the coupling patterns in diastereomers **13**−**18** and **19**−**21** is often complicated by a twist-boat conformation of six-membered ring owing to the ring fusion constraints. The overall stereostructure reveals an α configuration at both anomeric centers C-2 and C-6 based on the X-ray crystallographic analysis of the tandem cycloadduct **15** (see Supporting Information).[13] Again, crystal structure data support the existence of an anomeric effect at the pyranyl-like ring: bond lengths for O_{ring}−C and C−OEt are 1.430 and 1.407 Å, respectively. Furthermore, since similar coupling constants were found for the minor isomers **19** and **21**, their formation would have occurred through an opposite orientation in the [3 + 2] cycloaddition (Scheme 3, vide supra).

The three-component coupling in the presence of 1,4-benzoquinone deserves a particular consideration. Simply mixing the title compounds **12**, EVE, and 1,4-benzoquinone in ethanol at room temperature provided, after several days, the interesting tandem cycloadduct **22** in 41% yield (Scheme 4, Figure 1), in stark contrast with the reaction of **1** with EVE and 1,4-benzoquinone affording the single cycloadduct **8**. No other carbohydrate-based diastereoisomers were detected in the crude mixture by NMR analysis. Moreover, the latter revealed the existence of a diastereomerically pure sample. The spectroscopic analysis (see Experimental Section) also reveals a 2:2:1 nitroalkene:EVE:quinone ratio, consistent with the structure proposed for **22**. The NMR spectra of this complex molecule are extremely simple, a fact that evidences the equivalence of the two carbohydrate moieties and accounts for a symmetrical structure.

Although this material was isolated in crystalline form, no single crystals suitable for X-ray analysis could be obtained. Nevertheless, it is possible to propose a tentative stereostructure based on symmetry arguments and the well-known steric course of the tandem process.[3,9,10] There are eight possible structures which may be suggested to account for the tandem cycloadduct, as they will show only one signal set for the carbohydrate chain in their NMR spectra because of pairwise equivalence of the two frameworks around the quinone moiety. However, in four of them, the dipolar cycloaddition involves the si face of the nitronate intermediate, which leads to an additional steric crowding as revealed by inspection of CPK models. The remaining four molecular structures (**22A**−**D**) are shown in Figure 1 with the appropriate configuration of carbon atoms resulting from the stereochemical outcome. Both **22A** and **22C** have a 2-fold (C_2) axis passing through the two carbonyl groups, while structures **22B** and **22D** have a C_2 axis as well, which is perpendicular to a plane containing the quinone unit. On the other hand, it is also well-established that the stereochemical outcome of the [3 + 2] pathway proceeds invariably with exo orientation,[3,9] a fact that rules out the isomeric endo structures **22C** and **22D**. Thus, either **22A** or **22B** represent the most plausible molecular structures of this complex array. However, an additional argument in favor of **22A** stems from the fact that its formation would involve the attack of two EVE molecules from opposite faces, while **22B** would arise from addition to the same face of 1,4-benzoquinone, thereby creating a crowded transition state. Only X-ray analysis complemented with computational studies on the steric course could bring us one step nearer to solve definitively this question, and these studies are currently underway.

In the present study the facial selectivity is presumably due to steric effects from the chiral nitroalkene auxiliary. One would expect that these would be mitigated by both the longer distance between the reaction center and the first stereogenic centers of the side chain (which feature a relative threo arrangement in a D-galacto configuration), and the flexibility of the acyclic carbohydrate moiety.[22] Therefore, the energies of the competing transition structures must also be considered. The Coulombic interactions may also favor closer aproach of some atoms not directly involved in bond formation, which would then permit a greater steric differentiation of diastereomeric transition structures. Likewise, if because of an inherent asymmetric environment one side of the π orbital extends further into space than the other, it will overlap better with the approaching dienophile and therefore afford the forming bonds a greater degree of stabilization.[23]

Unmasking of the Nitrosoacetal. The formation of tandem cycloadducts from a carbohydrate precursor represent a further derivatization and elongation of nitroalkenyl sugars. Therefore, we were cognizant of the fact that such a cycloaddition, only *if rendered highly selective*, would be a convenient and expeditious strategy to higher carbon sugars. What remained to complete the homologation sequence was the liberation of the aldehyde group from the bicyclic system which also relieves ring strain. Knowing the well-documented acid-based protocols for acetal hydrolysis,[24] early studies were focused on the use of neat and aqueous mixtures of trifluoroacetic and acetic acids. Disappointingly, none of these conditions afforded clean deprotection of the bicyclic system and decomposition to a number of unidentified byproducts occurred. Likewise, hydrogenolysis of nitrosoacetals to α-hydroxy lactams[25] catalyzed by Raney nickel in methanol was unsuccessful and either decomposition took place or starting material was recovered. Several reasons for the failure of this reductive process can be invoked such as the competitive hydrogenolytic cleavage of ester groups of the auxiliary, as well as the ring strain created by recyclization after N−O bond cleavage, which can allow unwanted side reactions. Fortunately, subsequent studies demonstrated that the almost neutral conditions provided by refluxing cycloadducts in 50% aqueous ethanol selectively cleave the six-membered ring and leave the rest of the functional and protective groups untouched. Hence, tandem cycloadducts **13** and **16** were transformed into the corresponding aldehydes **23** and **24**, respectively, in quantitative yields. Such aldehydes also feature a stereodefined isoxazoline ring which can further be manipulated, especially for the preparation of chiral amino alcohols and aldol-type products.[26] The labile oily aldehyde **23** was further converted into its hydrazone derivative **25** which was isolated as a crystalline solid (Scheme 5). Current efforts are being addressed to the preparation of enantiopure furanoid and pyranoid sugars by cyclization of aldehydo sugars and their reaction with nucleophiles.

Conclusions

The formation of nitrogenated bicycles[27] through nitronate intermediates is an interesting synthetic methodology whose main operations involve the three-component coupling of nitroalkenes with electron-rich and electron-poor alkenes. This process complements the well-established sequential inter- or intramolecular cycloadditions

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(23) A full paper describing semiempirical, ab initio, and DFT studies on the stereodifferentiation of this tandem process, including the role of the chiral moiety, will be published elsewhere.

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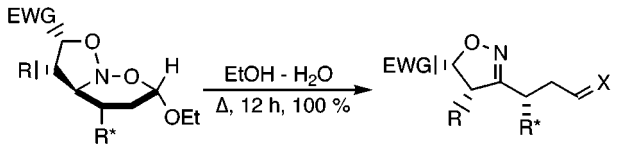
(26) For synthesis of isoxazolines by 1,3-dipolar cycloadditions, see: (a) Padwa, A. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Semmelhack, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1069−1109. (b) Wade, P. A. *Ibid*.; pp 1111−1168. (c) For a revision on chiral isoxazolines: Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293−318. (d) For a review on chiral isoxazolidines, see: Frederickson, M. *Tetrahedron* **1997**, *53*, 403−425.

Scheme 5. Carbohydrate Homologation by Cleavage of Tandem Nitrosoacetals



13, 16 **23-25**

13, 23 R = H, EWG = COOMe , X = O
16, 24 R = H, EWG = COMe, X = O
25 R = H, EWG = COOMe , X = N-NH-$C_6H_3(NO_2)_2$
R* = D-*galacto*-$(CHOAc)_4CH_2OAc$

of nitroalkenes either with alkenes or vinyl ethers. High levels of facial diastereoselection are observed in the uncatalyzed reactions of *β*-nitrostyrene (**1**) and the chiral nitroalkenyl sugar **12**, which produce endo/exo adducts as crystalline solids in good overall yields. Single-crystal X-ray analysis of cycloadduct **15** established unequivocally the structures of tandem cycloadducts, which were identical to that of products obtained in the reactions of chiral and racemic nitroalkenes with ethyl vinyl ether. Selective acetal deprotection under mild conditions gives rise to elongated acyclic sugars, which represents a notorious application of these chiral nitrosoacetals whose general utility must be explored in detail.

Experimental Section

General Methods. Melting points were determined on a capillary apparatus and are reported uncorrected. Reactions were monitored by TLC on silica gel 60 F_{254}; the positions of the spots were detected with 254-nm UV light and with iodine vapor. Flash chromatography[28] was performed on columns of silica gel (400−230 mesh) using ethyl acetate−hexane systems as eluents. Optical rotations were measured on a polarimeter at 20 °C in the stated solvent. IR spectra were recorded on KBr pellets with FT-IR spectrophotometers. ^{1}H and ^{13}C NMR spectra were recorded on a spectrometer operating at 400 and 100 MHz, respectively, at 20 °C in $CDCl_3$ unless otherwise specified. Chemical shifts are expressed in ppm positive values downfield from internal TMS, and apparent coupling constants are given in hertz. Elemental analyses were performed by the Servei de Microanàlisi del CSIC, Barcelona.

Reaction of *β*-Nitrostyrene with Ethyl Vinyl Ether. Synthesis of (±)-(2*R*,3a*R*,4*R*,6*S*)-2,6-Diethoxy-4-phenylperhydroisoxazolidino[2,3-*b*]-1,2-oxazine (2). To a suspension of **1** (0.50 g, 3.35 mmol) in anhydrous ethanol (15 mL) was added EVE (15 mL), and the reaction mixture was kept at room temperature for 10 days (TLC, ethyl acetate−hexane 1:4). The resulting solution was evaporated to dryness, and the residue was crystallized at 0 °C to give the title compound as white crystals (0.5 g, 51%): mp 75 °C; ^{1}H NMR *δ* 7.35−7.23 (m, 5H), 5.65 (d, *J* = 5.7 Hz, 1H), 4.92 (dd, *J* = 7.6, 6.8 Hz, 1H), 4.02 (m, 1H), 3.85−3.75 (m, 2H), 3.57 (m, 1H), 3.46 (m, 1H), 2.80 (m, 1H), 2.32−2.23 (m, 3H), 2.08 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.13 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR *δ* 141.8, 128.9, 127.4, 127.2, 107.6, 100.1, 72.8, 64.0, 63.5, 43.6, 37.8, 33.3, 15.1, 15.0. Anal. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90; N, 4.76. Found: C, 65.54; H, 7.98; N, 4.73.

Reaction of *β*-Nitrostyrene with Ethyl Vinyl Ether and Methyl Acrylate. Synthesis of (±)-(2*R*,3a*R*,4*R*,6*S*)-6-Ethoxy-2-methoxycarbonyl-4-phenylperhydroisoxazolidino[2,3-*b*]-1,2-oxazine (3) and (±)-(2*S*,3a*R*,4*R*,6*S*)-6-Ethoxy-2-methoxycarbonyl-4-phenylperhydroisoxa-zolidino[2,3-*b*]-1,2-oxazine (10). To a suspension of **1** (0.300 g, 2.0 mmol) in anhydrous ethanol (10 mL) were added EVE (6 mL) and methyl acrylate (6 mL). The reaction mixture was kept at room temperature for 20 days (TLC, ethyl acetate−hexane 1:4). The resulting solution was evaporated under reduced pressure, and the residue was purified by flash chromatography (ethyl acetate−hexane 1:6) to afford the title compounds as white solids, **3** (0.215 g, 35%) and **10** (0.050 g, 8%), along with starting *β*-nitrostyrene (0.007 g, 1%). Compound **3**: mp 68 °C; ^{1}H NMR *δ* 7.36−7.25 (m, 5H), 5.12 (dd, *J* = 9.6, 4.3 Hz, 1H), 4.96 (t, *J* = 7.2 Hz, 1H), 4.00 (m, 1H), 3.76 (m, 8.2 Hz, 1H), 3.72 (s, 3H), 3.57 (m, 1H), 2.88 (m, 1H), 2.56−2.46 (m, 2H), 2.24 (m, 1H), 2.09 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR *δ* 170.6, 141.5, 139.3, 128.9, 127.4, 127.2, 100.0, 80.9, 74.7, 63.0, 52.5, 44.0, 35.7, 33.1, 15.1. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.42; H, 6.88; N, 4.53. Compound **10**: mp 89 °C; ^{1}H NMR *δ* 7.37−7.21 (m, 5H), 5.07 (dd, *J* = 10.3, 2.9 Hz, 1H), 4.89 (dd, *J* = 9.4, 1.8 Hz, 1H), 4.06 (m, 1H), 3.80−3.63 (m, 3H), 3.70 (s, 3H), 2.63 (m, 1H), 2.07−1.91 (m, 2H), 1.74 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR *δ* 170.8, 139.3, 128.9, 127.4, 127.2, 100.2, 80.6, 71.6, 65.5, 52.4, 38.1, 29.9, 28.7, 15.2. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.52; H, 6.88; N, 4.52.

Reaction of *β*-Nitrostyrene with Ethyl Vinyl Ether and Dimethyl Maleate. Synthesis of (±)-(2*R*,3*S*,3a*R*,4*R*,6*S*)-6-Ethoxy-2,3-dimethoxycarbonyl-4-phenylperhydroisoxazolidino[2,3-*b*]-1,2-oxazine (4). To a suspension of **1** (0.200 g, 1.3 mmol) in anhydrous ethanol (5 mL) were added EVE (5 mL) and dimethyl maleate (5 mL). The reaction mixture was monitored by TLC (ethyl acetate−hexane 1:4) until the complete disappearance of the starting material (7 days). The resulting solution was concentrated under reduced pressure, and the residue was purified by chromatography (ethyl acetate−hexane 1:8, 1:4) affording the title compound as white crystals (0.143 g, 30%): mp 103 °C; ^{1}H NMR *δ* 7.34−7.23 (m, 5H), 5.29 (d, *J* = 9.7 Hz, 1H), 4.98 (t, *J* = 7.2 Hz, 1H), 4.09 (t, *J* = 8.6 Hz, 1H), 3.98 (m, 1H), 3.72 (s, 3H), 3.71 (m, 1H), 3.57 (m, 1H), 3.37 (s, 3H), 2.60 (m, 1H), 2.22 (m, 1H), 2.09 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR *δ* 169.6, 168.3, 140.8, 128.7, 127.5, 127.3, 100.0, 82.5, 78.1, 63.5, 53.8, 52.5, 52.2, 43.5, 33.5, 15.0. Anal. Calcd for $C_{18}H_{23}NO_7$: C, 59.17; H, 6.34; N, 3.83. Found: C, 59.02; H, 6.37; N, 3.87.

Reaction of *β*-Nitrostyrene with Ethyl Vinyl Ether and Acrylonitrile. Synthesis of (±)-(2*R*,3a*R*,4*R*,6*S*)-2-Cyano-6-ethoxy-4-phenylperhydroisoxazolidino[2,3-*b*]-1,2-oxazine (5) and (±)-(2*S*,3a*R*,4*R*,6*S*)-2-Cyano-6-ethoxy-4-phenylperhydroisoxazolidino[2,3-*b*]-1,2-oxazine (11). To a suspension of **1** (0.500 g, 3.3 mmol) in dry ethanol (10 mL) were added EVE (10 mL) and acrylonitrile (10 mL). The reaction mixture was kept at room temperature for 20 days until the disappearance of **1** (TLC, ethyl acetate−hexane 1:4). The solution was evaporated under reduced pressure, and the resulting residue was purified by chromatography (ethyl acetate−hexane 1:6) to give white crystals of **5** (0.453 g, 50%) and **11** (0.056 g, 6%). Compound **5**: mp 104 °C; ^{1}H NMR *δ* 7.39−7.25 (m, 5H), 5.22 (dd, *J* = 9.4, 4.6 Hz, 1H), 4.95 (t, *J* = 7.2 Hz, 1H), 3.97 (m, 1H), 3.88 (m, 1H), 3.57 (m, 1H), 2.87 (m, 1H), 2.69 (m, 1H), 2.56 (m, 1H), 2.22 (m, 1H), 2.11 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR *δ* 140.7, 129.1, 127.6, 127.3, 116.8, 100.2, 75.4, 69.1, 63.8, 43.7, 37.2, 33.2, 15.0. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.55; H, 6.67; N, 10.16. Compound **11**: mp 113 °C; ^{1}H NMR *δ* 7.40−7.21 (m, 5H), 5.18 (dd, *J* = 10.2, 3.0 Hz, 1H), 4.88 (dd, *J* = 8.2, 3.2 Hz, 1H), 4.02 (m, 1H), 3.87 (m, 1H), 3.72−3.64 (m, 2H), 2.71 (m, 1H), 2.04−1.88 (m, 3H), 1.26 (t, *J* = 7.1 Hz,

(27) The inherent complexity of the molecular systems obtained in this work constitutes a challenge to find out a consistent and unequivocal nomenclature. It has been possible to denote these substances in a satisfactory manner after an examination of the nomenclature currently available of 5,5,6-, 5,6,6-, and 5,6,6,6-fused ring systems. See for instance: *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Drayton, C. J., Eds.; Pergamon Press: Oxford, 1984; Vol. 8, Part 6 (Ring Index), pp 927−1111. A representation of the different polycyclic systems with the chemical numbering of the atoms has been incorporated as part of the Supporting Information.

(28) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

3H); ^{13}C NMR δ 138.5, 129.2, 127.8, 127.0, 117.1, 100.4, 72.5, 69.0, 63.6, 37.7, 30.3, 29.6, 15.1. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.49; H, 6.67; N, 10.23.

Reaction of *β*-Nitrostyrene with Ethyl Vinyl Ether and Maleic Anhydride. Synthesis of (±)-(3a*R*,7*S*,9*R*,9a*R*,9b*S*)-7-Ethoxy-9-phenylperhydrofuro[3′,4′:4,5]isoxazolidino-[2,3-*b*]-1,2-oxazine-1,3-dione (6). To a suspension of **1** (0.200 g, 1.34 mmol) in anhydrous ethanol (5 mL) were added EVE (5 mL) and maleic anhydride (0.26 g, 2.68 mmol). The reaction mixture was kept at ambient temperature for 13 days (TLC, ethyl acetate−hexane 1:4). The solution was evaporated under reduced pressure, and the residue was crystallized from diethyl ether to give **6** as a white solid (0.122 g, 30%): mp 145 °C; ^{1}H NMR δ 7.43−7.26 (m, 5H), 5.31 (d, J = 8.5 Hz, 1H), 4.89 (dd, J = 8.3, 6.4 Hz, 1H), 3.98−3.90 (m, 2H), 3.81 (t, J = 8.7 Hz, 1H), 3.60−3.51 (m, 2H), 2.26 (m, 1H), 2.11 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 168.7, 167.8, 140.8, 129.2, 127.7, 127.5, 100.9, 82.1, 79.6, 64.2, 47.2, 36.2, 32.5, 15.0. Anal. Calcd for $C_{16}H_{17}NO_5$: C, 60.18; H, 5.37; N, 4.38. Found: C, 59.80; H, 5.12; N, 4.48.

Reaction of *β*-Nitrostyrene with Ethyl Vinyl Ether and *N*-Phenylmaleimide. Synthesis of (±)-(3a*R*,7*S*,9*R*,9a*R*,-9b*S*)-7-Ethoxy-2,9-diphenylperhydropyrrolo[3′,4′:4,5]isox-azolidino[2,3-*b*]-1,2-oxazine-1,3-dione (7). To a suspension of **1** (0.200 g, 1.34 mmol) in anhydrous ethanol (5 mL) were added EVE (5 mL) and *N*-phenylmaleimide (0.460 g, 2.68 mmol), and the reaction mixture was kept at room temperature for 10 days. The resulting solution was diluted with diethyl ether and evaporated to dryness to give a residue that was crystallized from diethyl ether. Further recrystallization from ethyl acetate−hexane gave **7** (0.311 g, 59%): mp 184 °C; ^{1}H NMR δ 7.51−7.23 (m, 10H), 5.22 (d, J = 8.0 Hz, 1H), 4.86 (dd, J = 8.1, 6.5 Hz, 1H), 3.99−3.94 (m, 2H), 3.71−3.65 (m, 2H), 3.52 (m, 1H), 2.29 (m, 1H), 2.06 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 173.8, 172.6, 141.4, 131.5, 129.2, 128.9, 127.6, 127.3, 126.1, 100.7, 82.8, 78.6, 63.9, 46.4, 36.0, 32.6, 14.9. Anal. Calcd for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.55; H, 5.85; N, 7.22.

Reaction of *β*-Nitrostyrene with Ethyl Vinyl Ether and 1,4-Benzoquinone. Synthesis of (±)-(2*S*,4*R*,4a*R*,4b*S*,8a*R*)-2-Ethoxy-4-phenyl-2*H*,3*H*,4*H*,4a*H*,4b*H*,8a*H*-1,2-oxazino-[2,3-*b*]benzisoxazole-5,8-dione (8). To a suspension of **1** (0.200 g, 1.34 mmol) in anhydrous ethanol (5 mL) were added EVE (5 mL) and 1,4-benzoquinone (0.200 g, 1.88 mmol), and the reaction mixture was stirred at room temperature for 12 days. The resulting solution was evaporated under reduced pressure, and the residue was crystallized from diethyl ether to give the title compound (0.176 g, 40%): mp 120 °C; ^{1}H NMR δ 7.34−7.26 (m, 5H), 6.75 (d, J = 10.5 Hz, 1H), 6.62 (d, J = 10.5 Hz, 1H), 5.16 (d, J = 8.7 Hz, 1H), 5.02 (t, J = 6.9 Hz, 1H), 3.99 (m, 1H), 3.91 (t, J = 8.1 Hz, 1H), 3.71 (t, J = 8.1 Hz, 1H), 3.56 (m, 1H), 3.20 (m, 1H), 2.16−2.12 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 193.6, 190.7, 140.8, 140.6, 139.8, 128.7, 128.0, 127.3, 99.8, 80.9, 78.5, 63.6, 54.5, 42.7, 33.6, 15.0. Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.33; H, 5.69; N, 4.40.

Reaction of *β*-Nitrostyrene with Ethyl Vinyl Ether and 1,4-Naphthoquinone. Synthesis of (±)-(2*S*,4*R*,4a*R*,4b*S*,10a*R*)-2-Ethoxy-4-phenyl-2*H*,3*H*,4*H*,4a*H*,4b*H*,10a*H*-1,2-oxazino[2,3-*b*]naphthisoxazole-5,10-dione (9). To a suspension of **1** (0.500 g, 3.35 mmol) in dry ethanol (15 mL) were added EVE (7 mL) and 1,4-naphthoquinone (0.740 g, 4.68 mmol), and the reaction mixture was stirred at room temperature for 7 days. The resulting solution was evaporated to dryness, and the residue was crystallized from diethyl ether affording the title compound as a white solid (0.363 g, 28%): mp 136 °C; ^{1}H NMR δ 8.07−7.70 (m, 4H), 7.33−7.25 (m, 5H), 5.37 (d, J = 8.5 Hz, 1H), 5.05 (t, J = 6.8 Hz, 1H), 4.04−4.00 (m, 2H), 3.90 (t, J = 8.0 Hz, 1H), 3.57 (m, 1H), 3.29 (m, 1H), 2.19−2.13 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 192.4, 189.7, 141.0, 135.1, 135.0, 134.0, 133.5, 128.7, 128.0, 127.5, 127.2, 99.8, 82.2, 78.7, 63.6, 55.2, 42.6, 33.7, 15.0. Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.46; H, 5.30; N, 3.87.

Reaction of Nitroalkene 12 with Ethyl Vinyl Ether and Methyl Acrylate. Synthesis of (2*R*,3a*R*,4*S*,6*S*)-4-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-6-ethoxy-2-methoxycarbonylperhydroisoxazolidino[2,3-*b*]-1,2-oxazine (13) and (2*S*,3a*R*,4*S*,6*S*)-4-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-6-ethoxy-2-methoxycarbonyl-perhydroisoxazolidino[2,3-*b*]-1,2-oxazine (19). To a suspension of **12** (1.00 g, 2.31 mmol) in ethanol (20 mL) were added EVE (15 mL) and methyl acrylate (10 mL), and the reaction mixture was stirred at 25 °C for 4 days (TLC, ethyl acetate−hexane 1:1). The solution was evaporated to dryness, and the residue was crystallized from ethanol to give **13** (1.025 g, 75%) as a white solid. Further crystallization from the mother liquors afforded **19** (0.055 g, 4%). Compound **13**: mp 172 °C; $[\alpha]_D$ +63.4° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 5.32 (dd, J = 1.2, 10.0 Hz, 1H), 5.28−5.24 (m, 2H), 5.17 (dd, J = 2.0, 9.9 Hz, 1H), 5.01 (dd, J = 4.4, 9.3 Hz, 1H), 4.74 (t, J = 7.0 Hz, 1H), 4.33 (dd, J = 4.5, 11.8 Hz, 1H), 3.94 (m, 1H), 3.78 (dd, J = 7.6, 11.8 Hz, 1H), 3.75 (s, 3H), 3.52−3.43 (m, 2H), 2.36−2.28 (m, 2H), 2.18−2.15 (m, 1H), 2.13 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 1.84−1.71 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 170.5, 170.4, 170.2, 170.1, 170.0, 99.5, 80.9, 71.8, 69.7, 67.8, 67.7, 67.6, 63.4, 62.5, 52.5, 38.4, 35.7, 28.0, 20.7, 20.6, 15.0. Anal. Calcd for $C_{25}H_{37}NO_{15}$: C, 50.75; H, 6.30; N, 2.38. Found: C, 50.85; H, 6.31; N, 2.42. Compound **19**: mp 58 °C; $[\alpha]_D$ +3.5° (*c* 0.4, $CHCl_3$); ^{1}H NMR δ 5.30 (dd, J = 1.7, 9.7 Hz, 1H), 5.24−5.20 (m, 3H), 5.04 (dd, J = 4.0, 9.6 Hz, 1H), 4.77 (t, J = 6.8 Hz, 1H), 4.31 (dd, J = 4.8, 11.9 Hz, 1H), 3.91 (m, 1H), 3.81 (m, 1H), 3.78 (s, 3H), 3.63 (m, 1H), 3.47 (m, 1H), 2.56 (m, 1H), 2.33 (m, 1H), 2.13 (s, 3H), 2.12 (s, 3H), 2.09 (s, 6H), 2.02 (s, 3H), 2.12−2.02 (m, 1H), 1.82−1.77 (m, 2H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 170.4, 170.3, 170.0, 169.9, 99.5, 80.9, 70.1, 69.4, 68.8, 68.1, 67.7, 63.2, 62.3, 52.5, 38.1, 35.2, 26.8, 20.7, 20.7, 15.0. Anal. Calcd for $C_{25}H_{37}NO_{15}$: C, 50.75; H, 6.30; N, 2.38. Found: C, 50.81; H, 6.13; N, 2.31.

Reaction of Nitroalkene 12 with Ethyl Vinyl Ether and Dimethyl Maleate. Synthesis of (2*R*,3*S*,3a*R*,4*S*,6*S*)-4-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-6-ethoxy-2,3-dimethoxycarbonylperhydroisoxazolidino-[2,3-*b*]-1,2-oxazine (14). To a suspension of **12** (0.200 g, 0.46 mmol) in ethanol (10 mL) were added EVE (5 mL) and dimethyl maleate (4 mL), and the mixture was stirred at 25 °C for 7 days (TLC, ethyl acetate−hexane 1:1). The resulting solution was evaporated to dryness, and the residue was purified by chromatography using a gradient of ethyl acetate−hexane (0:1, 1:10, 1:5, 1:0) to give a crystalline mass (0.200 g), which was further recrystallized from ethanol to give the title compound (0.150 g, 50%): mp 160 °C, $[\alpha]_D$ +3.9° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 5.45 (d, J = 9.9 Hz, 1H), 5.37 (d, J = 9.9 Hz, 1H), 5.23−5.19 (m, 2H), 5.13 (dd, J = 9.9, 1.7 Hz, 1H), 4.84 (t, J = 5.2 Hz, 1H), 4.34 (dd, J = 4.2, 11.8 Hz, 1H), 3.95 (m, 1H), 3.80−3.69 (m, 2H), 3.74 (s, 6H), 3.60 (t, J = 9.6 Hz, 1H), 3.50 (m, 1H), 2.05−2.01 (m, 2H), 2.13 (s, 3H), 2.11 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.01 (s, 3H), 1.82 (m, 1H), 1.27 (t J = 7.0 Hz, 3H); ^{13}C NMR δ 170.5, 170.4, 170.4, 170.1, 169.8, 168.1, 99.2, 82.3, 71.4, 71.1, 67.9, 67.8, 63.2, 62.6, 52.5, 51.5, 35.5, 26.5, 20.9, 20.7, 15.0. Anal. Calcd for $C_{27}H_{39}NO_{17}$: C, 49.92; H, 6.05; N, 2.16. Found: C, 50.26; H, 6.01; N, 2.10.

Reaction of Nitroalkene 12 with Ethyl Vinyl Ether and Acrylonitrile. Synthesis of (2*R*,3a*R*,4*S*,6*S*)-4-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-2-cyano-6-ethoxyperhydroisoxazolidino[2,3-*b*]-1,2-oxazine (15) and (2*S*,3a*R*,4*S*,6*S*)-4-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-2-cyano-6-ethoxyperhydroisoxazolidino[2,3-*b*]-1,2-oxazine (20). To a suspension of **12** (0.200 g, 0.46 mmol) in ethanol (5 mL) were added EVE (5 mL) and acrylonitrile (5 mL), and the reaction mixture was stirred at 25 °C for 4 days. The resulting solution was evaporated under reduced pressure, and the residue was crystallized from ethanol to give a mixture of **15** and **20** (0.170 g). Fractional crystallization from ethanol afforded **15** (0.154 g, 60%). The minor isomer **20** (0.026 g, 10%) could be isolated after purification by flash chromatography (ethyl acetate−hexane 1:2). Compound **15**: mp 175 °C; $[\alpha]_D$ +64.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 5.32 (m, 2H), 5.25 (m, 1H), 5.17 (dd, J = 10.0, 1.7 Hz, 1H), 5.12 (dd, J = 7.6, 6.7 Hz, 1H),

4.74 (t, J = 6.5 Hz, 1H), 4.33 (dd, J = 4.4, 11.8 Hz, 1H), 3.91 (m, 1H), 3.78 (dd, J = 7.7, 11.8 Hz, 1H), 3.55 (m, 1H), 3.48 (m, 1H), 2.44 (t, J = 8.8 Hz, 2H), 2.14 (s, 3H), 2.13 (s, 3H), 2.12 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.85 (m, 1H), 1.84−1.73 (m, 2H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 170.4, 170.3, 170.1, 170.1, 169.9, 116.7, 99.7, 71.5, 70.2, 68.7, 67.7, 67.6, 63.6, 62.4, 38.1, 37.2, 27.4, 20.7, 20.7, 20.6, 15.0. Anal. Calcd for $C_{24}H_{34}N_2O_{13}$: C, 51.61; H, 6.14; N, 5.02. Found: C, 51.55; H, 6.15; N, 5.01. Compound **20**: mp 145 °C; $[\alpha]_D$ +116.7° (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 5.33 (dd, J = 9.9, 1.0 Hz, 1H), 5.29 (dd, J = 1.0, 10.1 Hz, 1H), 5.25 (m, 1H), 5.18 (dd, J = 1.7, 9.9 Hz, 1H), 4.92 (dd, J = 9.6, 6.3 Hz, 1H), 4.85 (t, J = 6.5 Hz, 1H), 4.33 (dd, J = 4.4, 11.8 Hz, 1H), 3.99 (m, 1H), 3.78 (dd, J = 7.7, 11.8 Hz, 1H), 3.54 (m, 1H), 3.42 (m, 1H), 2.60 (m, 1H), 2.44 (m, 1H), 2.15 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.05 (s, 3H), 1.94 (m, 1H), 1.75 (m, 2H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 170.4, 170.3, 170.1, 170.1, 170.0, 118.5, 99.7, 71.9, 70.5, 68.9, 67.7, 67.5, 63.8, 62.4, 38.5, 37.5, 27.6, 20.9, 20.7, 20.7, 15.0. Anal. Calcd for $C_{24}H_{34}N_2O_{13}$: C, 51.61; H, 6.14; N, 5.02. Found: C, 51.38; H, 6.12; N, 4.88.

Reaction of Nitroalkene 12 with Ethyl Vinyl Ether and Methyl Vinyl Ketone. Synthesis of (2*R*,3a*R*,4*S*,6*S*)-2-Acetyl-4-(1,2,3,4,5-penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-6-ethoxyperhydroisoxazolidino[2,3-*b*]-1,2-oxazine (16). To a suspension of **12** (0.200 g, 0.46 mmol) in ethanol (5 mL) were added EVE (5 mL) and methyl vinyl ketone (5 mL), and the reaction mixture was stirred at 25 °C for 6 days. The resulting solution was evaporated to a final volume of ∼5 mL, and then it was kept at 0 °C affording the title compound (0.185 g, 70%) as white crystals: mp 188 °C, $[\alpha]_D$ +7.7° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 5.32 (dd, J = 1.2, 9.9 Hz, 1H), 5.27−5.21 (m, 2H), 5.18 (dd, J = 9.9, 1.8 Hz, 1H), 4.90 (dd, J = 9.8, 4.6 Hz, 1H), 4.75 (t, J = 6.5 Hz, 1H), 4.32 (dd, J = 4.5, 11.8 Hz, 1H), 3.95 (m, 1H), 3.78 (dd, J = 7.6, 11.8 Hz, 1H), 3.51 (m, 1H), 3.30 (m, 1H), 2.32 (m, 1H), 2.26−2.16 (m, 2H), 2.21 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.83−1.70 (m, 2H), 1.27 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 206.2, 170.5, 170.3, 170.1, 169.9, 99.7, 87.9, 71.8, 69.7, 67.7, 67.6, 67.5, 63.6, 62.4, 38.7, 34.3, 28.0, 26.7, 20.7, 20.7, 20.6, 15.0. Anal. Calcd for $C_{25}H_{37}NO_{14}$: C, 52.17; H, 6.48; N, 2.43. Found: C, 52.02; H, 6.51; N, 2.43.

Reaction of Nitroalkene 12 with Ethyl Vinyl Ether and *N*-Phenylmaleimide. Synthesis of (3a*R*,7*S*,9*S*,9a*R*,9b*S*)-9-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-7-ethoxy-2-phenylperhydropyrrolo[3′,4′:4,5]isoxazolidino-[2,3-*b*]-1,2-oxazine-1,3-dione (17) and (3a*S*,7*S*,9*S*,9a*R*,9b*R*)-9-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-7-ethoxy-2-phenylperhydropyrrolo[3′,4′:4,5]-isoxazolidino[2,3-*b*]-1,2-oxazine-1,3-dione (21). To a suspension of **12** (0.200 g, 0.46 mmol) in ethanol (5 mL) were added EVE (5 mL) and *N*-phenylmaleimide (0.160 g, 0.92 mmol), and the mixture was stirred at 25 °C for 5 days. The resulting solution was diluted with diethyl ether and evaporated under reduced pressure to afford a residue that was crystallized from diethyl ether (0.200 g, 64%). The separation of both isomers was achieved by fractional crystallization from ethyl acetate−hexane to give **17** (0.110 g, 35%) and **21** (0.080 g, 25%). Compound **17**: mp 203 °C; $[\alpha]_D$ +1.02° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.49−7.42 (m, 3H), 7.27−7.25 (m, 2H), 5.49 (d, J = 9.4 Hz, 1H), 5.43 (m, 2H), 5.23 (m, 1H), 5.19 (dd, J = 1.7, 9.8 Hz, 1H), 4.92 (t, J = 5.3 Hz, 1H), 4.33 (dd, J = 4.5, 11.8 Hz, 1H), 3.97 (m, 1H), 3.80 (dd, J = 7.5, 11.8 Hz, 1H), 3.70 (m, 2H), 3.54 (m, 1H), 2.26−2.22 (m, 1H), 2.17−2.14 (m, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.02 (s, 3H), 1.82−1.77 (m, 1H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 173.2, 171.1, 170.5, 170.4, 170.1, 169.9, 130.9, 129.3, 129.0, 126.2, 99.2, 81.9, 72.6, 71.7, 67.8, 63.7, 62.5, 50.8, 36.6, 26.4, 21.2, 20.8, 20.8, 15.0. Anal. Calcd for $C_{31}H_{38}N_2O_{15}$: C, 54.86; H, 5.64; N, 4.13. Found: C, 54.56; H, 5.39; N, 4.16. Compound **21**: mp 188 °C; $[\alpha]_D$ +32.3° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 7.49−7.40 (m, 3H), 7.15−7.13 (m, 2H), 5.31 (m, 3H), 5.23 (m, 2H), 4.67 (t, J = 6.9 Hz, 1H), 4.31 (dd, J = 4.6, 11.6 Hz, 1H), 3.92−3.83 (m, 2H), 3.73 (m, 1H), 3.59 (t, J = 8.2 Hz, 1H), 3.46 (m, 1H), 2.81 (m, 1H), 2.16−2.11 (m, 1H), 2.17 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.00 (s, 3H), 1.87−1.80 (m, 1H), 1.23 (t, J = 7.1 Hz, 3H); ^{13}C NMR δ 173.6, 172.4, 170.7, 170.4, 170.0, 131.5, 129.2, 128.9, 126.0, 100.2, 82.5, 72.4, 71.9, 67.8, 63.1, 62.3, 46.8, 31.0, 28.5, 20.9, 20.7, 15.0. Anal. Calcd for $C_{31}H_{38}N_2O_{15}$: C, 54.86; H, 5.64; N, 4.13. Found: C, 54.49; H, 5.64; N, 4.13.

Reaction of Nitroalkene 12 with Ethyl Vinyl Ether and 1,4-Naphthoquinone. Synthesis of (2*S*,4*S*,4a*R*,4b*S*,10a*R*)-4-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-2-ethoxy-2*H*,3*H*,4*H*,4a*H*,4b*H*,10a*H*-1,2-oxazino[2,3-*b*]naphthisoxazole-5,10-dione (18). To a suspension of **12** (0.500 g, 1.15 mmol) in ethanol (10 mL) were added EVE (7 mL) and 1,4-naphthoquinone (0.250 mg, 1.61 mmol), and the reaction mixture was stirred at 25 °C for 6 days. The resulting solution was diluted with diethyl ether and evaporated under reduced pressure to give a residue that was crystallized from diethyl ether (0.380 g, 50%): mp 148 °C; $[\alpha]_D$ +27.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 8.14−8.08 (m, 2H), 7.85−7.83 (m, 2H), 5.72 (d, J = 9.9 Hz, 1H), 5.51 (d, J = 9.6 Hz, 1H), 5.30 (d, J = 9.3 Hz, 1H), 5.21 (m, 1H), 5.15 (dd, J = 1.9, 9.6 Hz, 1H), 4.94 (m, 1H), 4.31 (dd, J = 4.4, 11.8 Hz, 1H), 4.01 (m, 1H), 3.88−3.79 (m, 2H), 3.52 (m, 1H), 3.38 (dd, J = 9.7, 2.9 Hz, 1H), 2.42 (m, 1H), 2.21 (s, 3H), 2.10 (s, 6H), 2.02 (s, 3H), 2.13−2.05 (m, 1H), 1.87−1.82 (m, 1H), 1.82 (s, 3H), 1.29 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 192.9, 189.4, 170.5, 170.3, 170.2, 170.1, 170.0, 135.3, 135.0, 133.7, 127.8, 127.0, 99.3, 81.8, 72.8, 70.8, 67.9, 63.0, 62.5, 51.3, 34.2, 24.7, 20.8, 20.7, 20.6, 20.5, 15.0. Anal. Calcd for $C_{31}H_{37}NO_{15}$: C, 56.11; H, 5.62; N, 2.11. Found: C, 55.86; H, 5.56; N, 2.26.

Reaction of Nitroalkene 12 with Ethyl Vinyl Ether and 1,4-Benzoquinone. Synthesis of (2*S*,4*S*,4a*R*,4b*S*,5a*S*,5b*R*,6*S*,8*S*,11a*R*,12a*R*)-4,6-(1,2,3,4,5-Penta-*O*-acetyl-D-*galacto*-pentitol-1-yl)-2,8-diethoxybis[perhydro-1,2-oxazino-[2,3-*b*]isoxazolidino][4,5-*a*:4,5-*d*]cyclohexane-5,12-dione (22). To a suspension of **12** (0.200 g, 0.46 mmol) in ethanol (5 mL) were added EVE (5 mL) and 1,4-benzoquinone (0.110 g, 0.92 mmol), and the reaction mixture was stirred at 25 °C for 7 days. The solution was diluted with diethyl ether and evaporated to dryness to give a residue that was crystallized from diethyl ether (0.105 g, 41%): mp 196 °C; $[\alpha]_D$ +29.5° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 5.68 (d, J = 9.9 Hz, 1H), 5.42 (d, J = 9.7 Hz, 1H), 5.32 (d, J = 11.1 Hz, 1H), 5.21 (m, 1H), 5.15 (dd, J = 1.9, 9.7 Hz, 1H), 4.87 (m, 1H), 4.32 (dd, J = 4.3, 11.8 Hz, 1H), 3.94−3.88 (m, 1H), 3.82 (dd, J = 7.5, 11.8 Hz, 1H), 3.72 (t, J = 9.8 Hz, 1H), 3.49 (m, 1H), 2.19−2.05 (m, 2H), 2.12 (s, 3H), 2.11 (s, 3H), 2.09 (s, 3H), 2.08 (s, 3H), 2.01 (s, 3H), 1.87 (m, 1H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR δ 198.8, 197.4, 170.5, 170.4, 170.2, 170.1, 170.0, 99.3, 92.3, 85.4, 70.3, 68.0, 67.7, 63.1, 62.6, 54.3, 34.8, 24.4, 21.0, 20.8, 20.6, 15.0. Anal. Calcd for $C_{48}H_{66}N_2O_{28}$: C, 51.52; H, 5.94; N, 2.50. Found: C, 51.76; H, 5.94; N, 2.56.

Hydrolysis of 13. Synthesis of (5′*R*)-2,3-Dideoxy-4,5,6,7,8-penta-*O*-acetyl-3-(5′-methoxycarbonyl-2′-isoxazolin-3′-yl)-D-*glycero*-L-*gluco*-octose (23) and (5′*R*)-2,3-Dideoxy-4,5,6,7,8-penta-*O*-acetyl-3-(5′-methoxycarbonyl-2′-isoxazolin-3′-yl)-D-*glycero*-L-*gluco*-octose-2,4-dinitrophenylhydrazone (25). Compound **13** (0.125 g, 0.21 mmol) was dissolved in an ethanol−water mixture (1:1, 20 mL) which was refluxed for 5 h. The hydrolysis was monitored by TLC (ethyl acetate−hexane 1:1), and then the reaction mixture was evaporated under reduced pressure to give **23** (0.125 g, 100%) as a white solid that was further characterized through its 2,4-dinitrophenylhydrazone derivative. A solution of **23** (0.100 g, 0.18 mmol) in methanol (10 mL) was treated with 2,4-dinitrophenylhydrazine (0.040 g, 0.20 mmol), and the reaction mixture was stirred at room temperature overnight. The solvent was evaporated, the resulting residue was dissolved in ethyl acetate (40 mL), and the organic layer was washed successively with 10% sulfuric acid, 5% sodium hydrogen carbonate, and water. The organic phase was dried over magnesium sulfate and filtered, and the solvent was evaporated. The residue was treated with ethanol and ethyl acetate, and the mixture was heated, which produced the crystallization of **25** as orange crystals (0.060 g, 45%): mp 175 °C; $[\alpha]_D$ +67.5° (*c* 0.3, $CHCl_3$); ^{1}H NMR δ 11.03 (s, 1H), 9.10 (d, J = 2.6 Hz, 1H), 8.32 (dd, J = 9.4 Hz, 1H), 7.87 (d, J = 9.6 Hz, 1H), 7.42 (t, J = 4.3 Hz, 1H), 5.50 (dd, J = 1.8, 9.8 Hz, 1

H), 5.33−5.24 (m, 3H), 4.94 (dd, J = 6.8, 11.6 Hz, 1H), 4.30 (dd, J = 4.7, 11.7 Hz, 1H), 3.80 (m, 1H), 3.60 (s, 3H), 3.39−3.19 (m, 3H), 2.94 (m, 1H), 2.60 (m, 1H), 2.12 (s, 6H), 2.10 (s, 3H), 2.09 (s, 3H), 2.03 (s, 3H); ^{13}C NMR δ 170.6, 170.4, 170.2, 169.7, 157.3, 146.6, 144.8, 138.2, 130.0, 129.2, 123.3, 116.7, 69.3, 68.0, 67.8, 67.5, 62.1, 52.7, 38.5, 37.3, 31.9, 20.7, 20.6. Anal. Calcd for $C_{29}H_{35}N_5O_{17}$: C, 48.00; H, 4.86; N, 9.65. Found: C, 47.78; H, 5.00; N, 9.47.

Hydrolysis of 16. Synthesis of (5′*R*)-2,3-Dideoxy-4,5,6,7,8-penta-*O*-acetyl-3-(5′-acetyl-2′-isoxazolin-3′-yl)-D-*glycero*-L-*gluco*-octose (24). Compound **16** (0.200 g, 0.38 mmol) was dissolved in ethanol−water (1:1, 20 mL), and the reaction mixture was refluxed for 8 h. The resulting solution was evaporated under reduced pressure to give **24** (0.200 g, 100%) as a white solid: mp 147 °C; $[\alpha]_D$ −31.4° (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 9.65 (s, 1H), 5.37 (dd, J = 1.4, 11.0 Hz, 1H), 5.25−5.19 (m, 3H), 4.79 (dd, J = 5.6, 11.5 Hz, 1H), 4.28 (dd, J = 4.7, 11.7 Hz, 1H), 3.78 (dd, J = 7.5, 11.7 Hz, 1H), 3.29−3.18 (m, 2H), 3.12 (dd, J = 5.6, 17.4 Hz, 1H), 2.96 (dd, J = 5.0, 18.3 Hz, 1H), 2.82 (dd, J = 9.3, 18.3 Hz, 1H), 2.27 (s, 3H), 2.10 (s, 9H), 2.07 (s, 3H), 2.02 (s, 3H); ^{13}C NMR δ 207.8, 198.1, 170.5, 170.3, 170.0, 169.8, 158.1, 67.9, 67.7, 67.4, 62.2, 43.3, 38.4, 33.5, 26.4, 20.7, 20.6. Anal. Calcd for $C_{23}H_{31}NO_{13}\cdot H_2O$: C, 50.45; H, 6.07; N, 2.55. Found: C, 50.63; H, 5.77; N, 2.57.

X-ray Crystal Structure Determination.[13] X-ray measurements were made on crystals of the appropriate size, which were mounted on a capillary and transferred to a Siemens P4 automatic diffractometer at 298 K, using Mo Kα graphite-monochromated radiation. The structures were solved by the program SHELXTL-IRIS[29] on the basis of direct methods and refined using a full-matrix least-squares method. Data were collected employing the $2\theta-\theta$ scan technique. Three standard reflections measured every 97 reflections showed no significant variations. The hydrogen atoms were located from a differential Fourier synthesis and included in the calculation with estimated isotropic displacement parameters without refinement.

Acknowledgment. We gratefully acknowledge the Ministerio de Educación y Cultura of Spain (DGICYT, Project PB95-0259-CO2-01) and the Junta de Extremadura-Fondo Social Europeo (PRI97-C175) for financial support. We also thank Consejería de Educación y Juventud-Junta de Extremadura for a fellowship to M.A.S.

Supporting Information Available: X-ray structural data for compounds **2** and **15**, including tables of atomic coordinates, bond lengths, and bond angles, as well as a representation of the different polycyclic systems with the chemical numbering of the atoms, which is maintained through the Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

JO981921J

(29) Sheldrick, G. M. SHELXTL-IRIS, Release 4.2; Siemens Analytical X-ray Instruments, Inc., Madison, WI, 1991.