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ON THE STEREOSELECTIVITY OF NITRONE ADDITION TO (R)-4-O-BENZYL-4-HYDROXY-2-PENTEN-5-OLIDE

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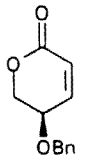
The title reaction was investigated for both known achiral and new chiral optically pure nitrones. In all cases, formation of only two diastereomeric cycloadducts was observed.

The 1,3-dipolar cycloaddition reaction between an alkene and a nitrone leading to isoxazolidines is an important reaction in organic chemistry [1]. The isoxazolidines formed by this reaction can easily be converted into a variety of different building blocks such as γ-amino alcohols, and the isoxazolidine route has often been used for the preparation of a variety of different products [2]. The optimal goal for this cycloaddition is to control both the *endo/exo* stereoselectivity and the enantioselectivity [3, 4].

With our efforts to utilize heterocyclic compounds as dipolarophile components in 1,3-dipolar cycloaddition, this paper is devoted to the synthesis and 1,3-dipolar cycloaddition of chiral and achiral nitrones to (R)-4-O-benzyl-4-hydroxy-2-penten-5-olide (**1**), keeping in mind that the N—O bond in the expected cycloadducts can be readily cleaved [5].



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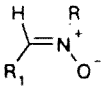
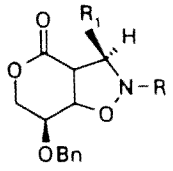


2

The cycloadditions of optically active lactone **1**, which was prepared from 4-O-benzyl-4,5-dihydroxy-2-pentenoate according [6], to achiral nitrones **2**, at reflux temperature in benzene for 6-30 h gave the corresponding bicyclic isoxazolidines **3** and **4** in moderate to good yields with the exclusive regioselectivity. In all the reactions studied, only two diastereomeric products **3** and **4** were formed and their ratio was established by integration of ^{1}H NMR spectra of the crude reaction mixtures. The corresponding regioisomer **5** was not detected in the crude reaction mixture.



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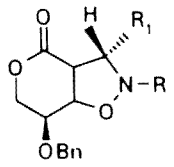

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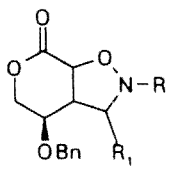

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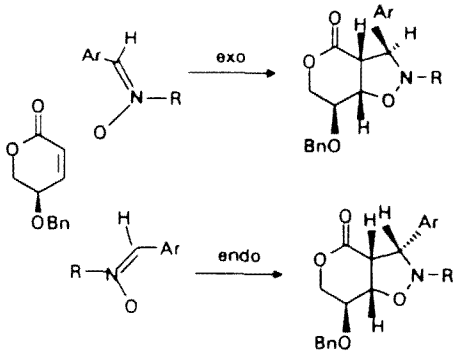
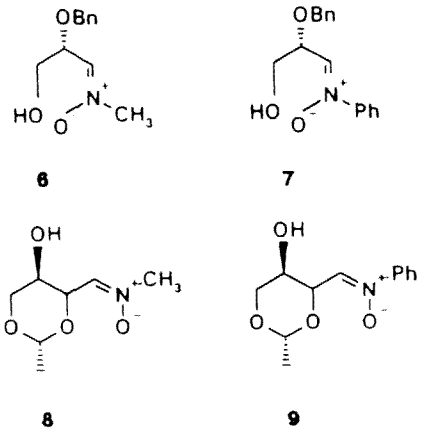
The diastereoselectivity for cycloadditions to the lactone **1** was found to be 57:43 for C-(4-nitrophenyl)-N-phenyl nitrone and 69:31 (C,N-diphenyl nitrone), the highest *endo/exo* ratio, >95:5 was obtained for the reaction of **1** with C-phenyl-N-methyl nitrone.

The structural assignment to cycloadducts **3** and **4** was based on the detailed ^{1}H and ^{13}C NMR analysis, including 2D experiments. Both diastereoisomers **3** and **4** were formed from the highly preferred approach of the nitrone **2** *anti* to the O-benzyl group in the transition state. The formation of both epimers could be explained through the following *endo* and *exo* approach. Three new chiral centers were generated in the cycloaddition, therefore the stereochemical outcome of this reaction is very remarkable.



The utility of nitrones as useful synthetic intermediates that are known to react with organometallic reagents [7-9], as well as with alkenes [1, 10, 11], has been extensively demonstrated. However, in spite of that well-documented utility, there are only scattered reports dealing with the preparation of nitrones possessing a chiral rest on their carbon substituent [3, 12]. During the course of our studies, Dondoni et al. presented their results regarding the preparation of chiral N-benzyl nitrones [13]. This result strongly motivated us to prepare such a class of chiral (Z)-nitrones **6-9** that bear the unprotected hydroxyl group controller and to examine cycloaddition reactions. To our best knowledge, there have been no reports concerning the synthesis of chiral nitrones **6-9**.



6 **7**

8 **9**

The desired nitrone **6** was prepared from the corresponding aldehyde [5] (readily available from L-diethyl tartrate), which was condensed with N-methylhydroxylamine in ethanol in the presence of potassium carbonate to afford the rather stable nitrone **6** as a single isomer in 83% yield. The N-methyl nitrone **8** was prepared (55%) starting from D-glucose from the corresponding aldehyde [14] by a procedure similar to that employed for nitrone **6** but using DABCO as a base.

A single isomer was obtained in each case and the expected Z configuration was confirmed by nuclear Overhauser effect difference spectroscopy (NOEDS), which showed an enhancement of N-methyl signal in **6** and **8** upon irradiation of the azomethine hydrogen, as well as an enhancement of the azomethine proton signal upon irradiation of the methyl group.

The mentioned readily available starting chiral aldehydes were further converted into the N-phenyl nitrones **7** (46%) and **9** (63%) by reaction with phenylhydroxylamine in ethanol. Nuclear Overhauser effect difference spectroscopy supported the Z configuration of **7** and **9**.

Nitrones **6-9** react also with lactone **1** regiospecifically and *anti* to the O-benzyl substituent to give the corresponding cycloadducts **3** and **4** in good yield. In all cases N-methylnitrones reacted with higher diastereoselectivity than the corresponding N-phenyl analogues. On the other hand, the nitrone **6** gave the sole product **3**.

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