PRELIMINARY COMMUNICATION

Stereoselectivity of *N*-Benzyl-*C*-ethoxycarbonyl Nitrone Cycloaddition to (*S*)-5-Hydroxymethyl-(5*H*)-furan-2-one

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In the course of our research concerning with synthesis of natural products, we planned an efficient strategy for the preparation of polyhydroxylated derivatives of piperidine, pipecolinic acid (*I*) [1] *via* an asymmetric 1,3-dipolar cycloaddition between a nitrone and chiral heterocyclic dipolarophile, (*S*)-5-hydroxymethyl-(5*H*)-furan-2-one (*II*) [2]. Asymmetric nitrone 1,3-dipolar cycloadditions involving the use of chiral dipolarophiles have received only limited attention [3—6]. Recently, we have described the nitrone cycloadditions to chiral (4*R*)-4-*O*-benzyl-4-hydroxy-2-penten-5-olide, where in all cases formation of only two diastereomeric cycloadducts was observed [7]. Stereoselective cycloaddition of cyclic achiral nitrone *III* with sugar lactone *II* (Scheme 1) has been reported [8]. With our efforts to utilize heterocyclic compounds as dipolarophile component in 1,3-dipolar cycloaddition this prompted us to publish preliminary results on the regio- and stereochemical outcome of the nitrone cycloaddition to lactone *II*, having in mind that the N—O bond in the expected cycloadducts can be readily cleaved [9], to obtain a precursor for the synthesis of *I*, together with the improved procedure for the preparation of sugar lactone *II*.

Despite the synthetic and mechanistic importance of sugar lactones, there are relatively few methods for their preparation [8]. *Jäger et al.* have synthesized lactone *II* by utilizing D-mannitol as commercially available chiral precursor *via* lactonization of (*Z*)-ethyl-(*S*)-4,5-dihydroxy-4,5-*O*-isopropylidene-2-pentenoate ((*Z*)-*V*) with H_2SO_4 in 63 % yield (Scheme 2). We have improved this procedure (85 % yield by larger scale) by prolonged reaction time (1.5 h), addition of equimolar amount of water and by using neutralization with NaOH, instead of Lewatit MP 62, to pH 6.

The cycloaddition of the so prepared optically active lactone *II*, to achiral *N*-benzyl-*C*-ethoxycarbonyl nitrone *VI*, at reflux temperature in benzene for 6 h gave the chromatographically separable bicyclic isoxazolidines *VII* and *VIII* in 60 % yield with the exclusive regioselectivity. The starting nitrone *VI* was prepared from corresponding aldehyde [10] (readily available from L-diethyl tartrate), which was condensed with *N*-benzylhydroxylamine in dichloromethane in the presence of magnesium sulfate [11]. There are eight possible products, *exo*- and *endo*-isomers for each pair of regioisomers resulting from *anti* and *syn* face attack related to hydroxymethyl group. Only two diastereomeric products *VII* and *VIII*, the oxygen of the 1,3-dipole becoming attached to the β-carbon of the enone unit, were formed and their ratio (w_r = 57:43) was established by integration of ^{1}H NMR spectra of the crude reaction mixtures. Neither the corresponding regioisomer *IX* nor any of the other five possible adducts were detected in the crude reaction mixture (Scheme 3).

The structural assignment (new compounds were characterized by their NMR spectra and their elemental compositions established by combustion analysis, only selected ^{1}H NMR data are given) to cycloadducts *VII* (m.p. = 150—153 °C, [α](D, 23 °C, ρ = 5.1 g dm^{-3} in $CHCl_3$) = + 123° ^{1}H NMR spectrum ($CDCl_3$), δ: 3.77 (1H, dd, $J_{3a,6a}$ = 7.6 Hz, H-3a), 3.79 (1H, d, $J_{3,3a}$ = 7.8 Hz, H-3), 3.89 (2H, m, CH_2), 3.92 (1H, dd, J = 2.4 and 12.4 Hz, $\underline{CH_2}OH$), 4.24 (3H, m, CH_2), 4.57 (1H, d, $J_{6,6a}$ = 1.9 Hz, H-6), 4.87 (1H, dd, H-6a)) and *VIII* (m.p. = 80—81 °C, ^{1}H NMR spectrum ($CDCl_3$),

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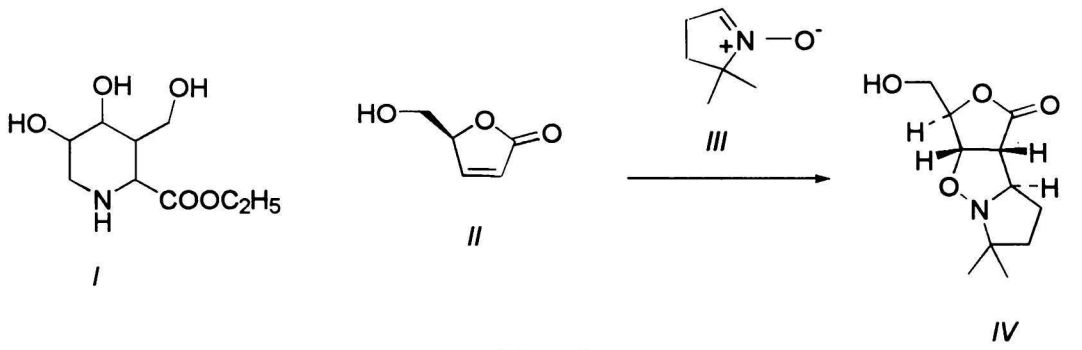
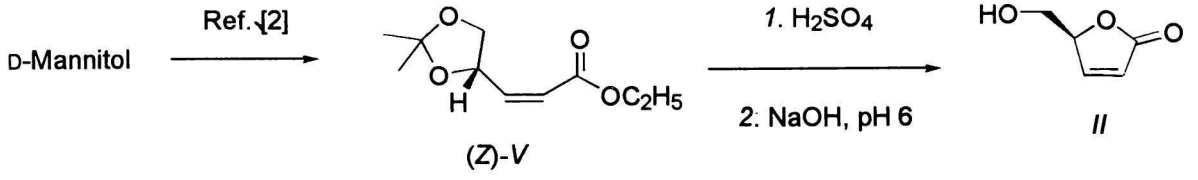
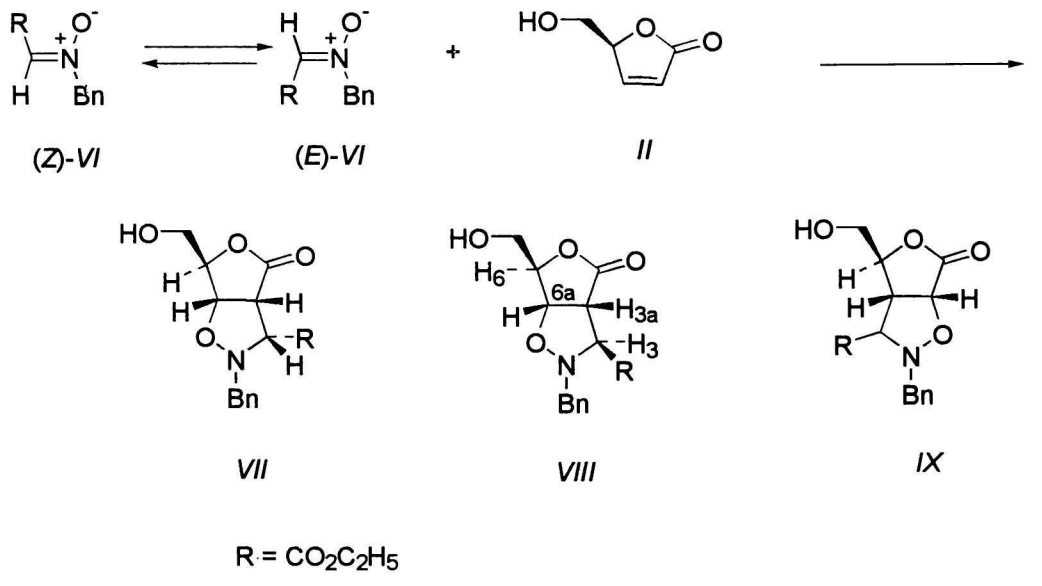


Scheme 1



Scheme 2



Scheme 3

δ: 3.70 (1H, dd, J = 2.4 and 12.6 Hz, $\underline{CH_2}OH$), 3.87 (1H, dd, J = 2.7 and 12.6 Hz, $\underline{CH_2}OH$), 3.89 (1H, d, $J_{3,3a}$ = 2.7 Hz, H-3), 3.95 (1H, dd, $J_{3a,6a}$ = 6.6 Hz, H-3a), 4.16 (4H, m, 2 × CH_2), 4.55 (1H, m, H-6), 4.77 (1H, d, H-6a)) was based on the detailed ^1H and ^{13}C NMR analysis including 2D experiments.

The proton H-6a (δ = 4.87 for *VII* and 4.77 for *VIII*) resonates at lower field as compared to the proton H-3a. Stereochemical assignments of H-3, H-3a, and H-6a atoms of these condensed isoxazolidines were made on the basis of the $J_{3,3a}$ and $J_{3a,6a}$ coupling constant. The ring junction between two rings was always *cis*, which was indicated by coupling constants. Moreover, all up-to-date known 1,3-dipolar cycloadditions of nitrones to alkenes proceeded with *cis* stereospecificity [3]. For instance, in the compound *VII* the coupling constant for the *cis* ring junction protons H-6a and H-3a was $J_{3a,6a}$ = 7.6 Hz and in *VIII* $J_{3a,6a}$ = 6.6 Hz, which is indicative of nearly eclipsed dihedral angles between H-3a and H-6a.

Proton NMR analysis of isoxazolidines *VII* and *VIII* revealed that both diastereoisomers have a H-6, H-6a *anti* relationship; *e.g.* in *VII*, the signal for H-6a proton appears as a doublet of doublets at δ =

4.87 with coupling constants of $J_{3a,6a}$ = 7.6 Hz and $J_{6,6a}$ = 1.9 Hz. In the H-6, H-6a *anti*-adducts the protons H-6 and H-6a display a small value of coupling constant since $\phi \approx 90°$ This feature of NMR spectrum is uniquely diagnostic of the H-6, H-6a *anti* relationship [12]. In *VIII* the coupling constant between bridgehead H-3a and isoxazolidine H-3 ($J_{3,3a}$ = 2.7 Hz) is consistent only with *anti* stereochemistry, since in a *syn*-isomer *VII* the two hydrogens would be nearly eclipsed and would give rise to a much larger coupling constants. Indeed, the isolated adduct *VII* showed $J_{3,3a}$ = 7.8 Hz, which is in the range expected for a H-3, H-3a *syn* relationship. Further support for this *syn* relationship is the signal for the H-3a proton appearing as doublet of doublets [13].

Both diastereoisomers *VII* and *VIII* were formed from a highly preferred approach of the nitrone *VI* *anti* to the hydroxymethyl group in the transition state. The isomer ratio of nitrone *VI* cycloaddition to *II* was dependent upon the reaction solvent used: *w*(*VII*):*w*(*VIII*): 57:43 (benzene), 34:66 (CH_2Cl_2), 27:73 (DMSO), and 45:55 (methanol). Nitrone *VI* as ester-conjugated nitrone exists as *E*—*Z* mixture at room temperature, the isomer ratio $w(E)/w(Z)$ = 66:34 in deuteriochloroform. Thus, the stereoselectivity observed in these nitrone cycloadditions reflected on the $w(E)/w(Z)$ isomer ratio of *VI*, further investigation on this unusual phenomenon is in progress.

In conclusion, the degree of selectivity in this reaction is remarkably high. Nitrone *VI* undergoes highly regio- and face-selective cycloaddition reaction with *II*, the products result from the approach *anti* to the hydroxymethyl group of *II*, and the oxygen of the 1,3-dipole becomes attached to the β-carbon of the enone unit. Comparable selectivity for mesitylcarbonitrile oxide was also found by *Jäger et al.* [14]. Thus, furanone *II* as a reactive and readily available dipolarophile, is being proved to be a valuable precursor for the preparation of polyhydroxylated derivatives of piperidine.

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