Pergamon

Tetrahedron 55 (1999) 10425–10436

TETRAHEDRON

# Stereoselectivity of *N*-Benzyl-*C*-ethoxycarbonyl Nitrone Cycloaddition to (*S*)-5-Hydroxymethyl-2(5*H*)-furanone and Its Derivatives

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Received 24 February 1999; revised 7 June 1999; accepted 25 June 1999

**Abstract**: Stereoselectivity of the reaction of *N*-benzyl-*C*-ethoxycarbonyl nitrone (**3**) with (*S*)-5-hydroxymethyl-2(5*H*)-furanone (**2a**) and its 5-alkoxy substituted derivatives **2b-f** was investigated. The reaction proceeds in a highly face-selective manner, the products **4-6** resulting from approach *anti* to the hydroxymethyl or alkoxymethyl group of the dipolarophile. The *exo*-stereoselectivity increases as the size of protective group attached to lactone (**2b-f**) increases. *Endo-exo* diastereoselectivity is affected significantly by the solvent. Microwave irradiation strongly accelerates the reaction with little effect on the diastereoselectivity to give the *syn* adduct **8a** in addition to *anti* cycloadducts **4a-6a.** 

*Keywords: Nitrones; cycloadditions; stereoselection; isoxazolidines; microwave heating*

*This paper is dedicated to Professor Fumio Toda on the occassion of his 65th birthday*

## INTRODUCTION

The nitrone-olefin 1,3-dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centers in a single step. Based on an evaluation of the nitrone cycloaddition,[1] it was felt that the stereochemistry of these new centers could be controlled if the reaction system was properly designed. Asymmetric nitrone 1,3-dipolar cycloadditions involving the use of chiral dipolarophiles have been described.[2,3] With the goal of developing a simple route to

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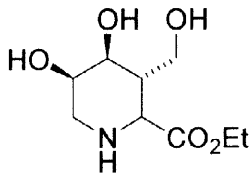
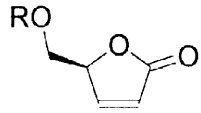
*PII:* S0040-4020(99)00568-2

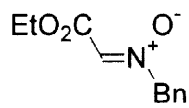
polyhydroxylated derivatives (**1**)[4] of pipecolinic acid *via* an asymmetric 1,3-dipolar cycloaddition, we have designed (*S*)-5-hydroxymethyl-2(5*H*)-furanone (**2a**) and its 5-alkoxy substituted derivatives **2b-f** as templates for nitrone cycloadditions. Our preliminary results in the cycloadditions to **2a** have been the subject of a recent communication.[5] In this paper we report on the factors which control the stereoselectivity of the reaction of *N*-benzyl-*C*-ethoxycarbonyl nitrone (**3**) with optically active lactones **2a-f**, having in mind that the N–O bond in the cycloadducts can be readily cleaved[6] to obtain a precursor for the synthesis of polyhydroxylated piperidine derivatives such as **1**.




**1**




**2a-f**




**3**

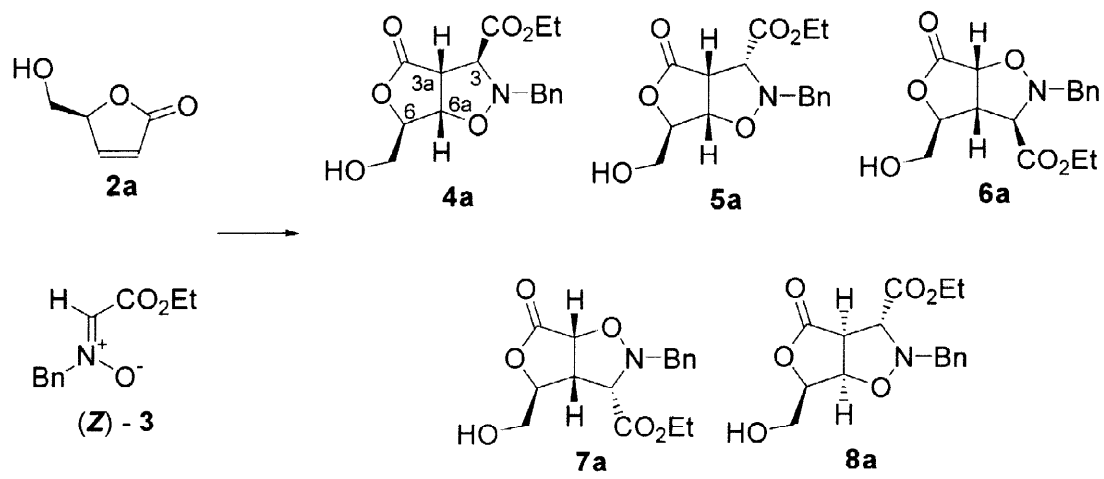
**a** R = H **d** R = Pv
**b** R = Ac **e** R = TBDMS
**c** R = Bz **f** R = TBDPS

## RESULTS AND DISCUSSION

Cycloaddition of the nitrone **3** to the lactone **2a** in boiling benzene for 6 h gave a 53 : 37 : 10 mixture of three optically active adducts **4a-6a** in 66 % combined yield, each of which was separated by flash chromatography. There are eight possible products, comprising *exo*- and *endo*-isomers for each pair of regioisomers resulting from *anti* and *syn* face attack related to the hydroxymethyl group. Only diastereomeric adducts **4a** and **5a**, in which the oxygen of the 1,3-dipole has become attached to the β-carbon of the enone unit, together with regioisomeric cycloadduct **6a** were formed. The $^1$H NMR spectra of **4a-6a** were well resolved, and confirmed the indicated regiochemistry for the reaction. Neither *anti*-**7a** nor any of the other four possible *syn* adducts were detected in the crude reaction mixture (Scheme 1).

The relative configuration at C-3, C-3a, C-6a and C-6 in the major adduct **4a** could be unambiguously assigned on the basis of NOEDS results (nuclear Overhauser enhancement difference spectroscopy). In particular, mutual interactions were observed between H-6a and H-3a, between H-6a and $CH_2$ of the hydroxymethyl substituent, and H-3 showed interactions with H-6.

Retention of the configuration of the dipolarophile **2a** upon cycloaddition requires H-3a and H-6a should be in **a** *cis* relationship. A coupling constant, $J_{3a,6a}$ = 6.6 Hz, which is indicative of nearly eclipsed C-H bonds supports this assignment. Moreover, other 1,3- dipolar cycloadditions of nitrones




**Scheme 1**

to alkenes are known to proceed with *cis* stereospecificity.[1] $^1$H NMR analysis of isoxazolidine **4a** also indicated an H-6, H-6a *anti* relationship; the signal for H-6a appearing as a doublet with a coupling constant of $J_{3a,6a}$ = 6.6 Hz. In the *anti* adducts the absence of detectable coupling constant between H-6 and H-6a is consistent with a dihedral angle $\theta \approx 90°$ between these C-H bonds. The relative stereochemistry between H-3 and H-3a is assigned on the basis of the magnitude of the vicinal coupling constant $J_{3,3a}$ = 2.7 Hz which is consistent with an *anti* arrangement of these C-H bonds.

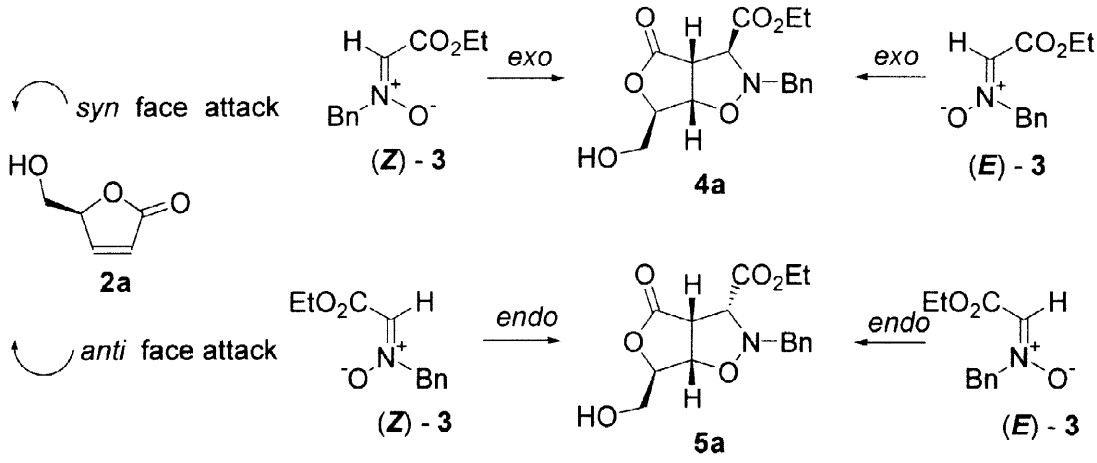
The $^1$H NMR spectrum of **5a** could be assigned by COSY analysis, and the stereochemistry again became apparent from NOE experiments. In particular, interactions were observed on the convex face of the molecule between H-3, H-3a and H-6a. That **5a** has the same relative H-6, H-6a *anti*-stereochemistry as **4a** is inferred from the close agreement of the chemical shift and coupling constants of the key H-6 and H-6a signals; in **5a** the signal for H-6a appears as a doublet of doublet with coupling constants of $J_{3a,6a}$ = 7.6 Hz and $J_{6,6a}$ = 1.9 Hz. The coupling constant $J_{3,3a}$ = 7.8 Hz, is in the range expected for an H-3, H-3a *syn* relationship. Further support for this *syn* relationship comes from the signal for H-3a appearing as doublet of doublets.[7]

Surprisingly, in this case, a small amount of another regioisomer **6a** (10 %) was also obtained after chromatography. The $^1$H NMR spectrum of **6a** was well resolved, and connectivities could be established by COSY experiments. This reversed regiochemistry was supported by the resonance position and multiplicity for the H-3a and H-6a signals; in **6a** the signal for H-3a appears as a ddd with coupling constants $J_{3,3a}$ = 4.0 Hz, $J_{3a,4}$ = 1.8 Hz and $J_{3a,6a}$ = 8.2 Hz, whilst the signal for H-6a appears as a doublet. NOE data are fully in accord with the these assignments. In particular, on the convex face of the compound, H-3a interacted strongly with H-6a and with the side-chain $CH_2$ group, whilst irradiation of H-6a showed enhancement of both the H-3a and the $CH_2$ signals.

Formation of the diastereoisomers **4a-6a** can be rationalized by involving a highly preferred approach of the nitrone **3** *anti* to the hydroxymethyl group in the transition state (Scheme 2). The dominance of the *anti*-mode of cycloaddition, accords with previous findings for cycloadditions of **2a** with a cyclic nitrone[3a] and *C,N*-diarylnitrones[3b] and comparable selectivity for mesitonitrile oxide was also found by Jäger *et al.*[8] The high face-selectivity observed in the generation of each diastereoisomer **4a-6a** can be rationalized following inspection of Dreiding models. The transition states leading to the formation of the *anti* **4a-6a** experience no steric encumbrance when the dipole **3** approaches the lower face of the dipolarophile **2a** in an *anti* orientation and cycloadditon proceeds exclusively by this mode. Clearly steric factors are important in orientating the dipole **3** in the cycloaddition.

The isomer ratio of nitrone **3** cycloaddition to **2a** was found to be dependent upon the reaction solvent used (Table 1). Three structural features can influence the stereochemical outcome of nitrone/alkene cycloadditions: *E/Z* nitrone isomerization about the C=N bond, alkene(nitrone) facial selectivity, and *endo/exo* preferences.[1] The formation of both major epimers **4a** and **5a** could be explained through the following *endo* and *exo* approach (Scheme 2), the isoxazolidine **4a** arising from cycloaddition of *Z*-nitrone and *E*-nitrone through an *exo* transition state. On the other hand, the adduct **5a** could be formed by the *Z*-nitrone and *E*-nitrone reacting in the *endo*-fashion. [9] Nitrone **3**, an ester-conjugated nitrone exists as an *E/Z* mixture in solution.[10] In contrast to previous reports giving the *E/Z* isomer ratio at room temperature,[10] we report now the *E/Z* ratio at reaction temperature (Table 1). We showed that, there was no thermal interconversion between the three adducts **4a-6a** even in refluxing toluene, thus indicating that the cycloaddition proceeds irreversibly under the reaction conditions to give the kinetically controlled products **4a-6a**. Thus, the stereoselectivity observed in these cycloadditions reflects not only the steric hindrance in the corresponding *exo/endo* transition states but also the tendency of this nitrone to undergo the *E/Z* isomerization reaction. *Endo/exo* diastereoselectivity of *C,N*-diarylnitrone cycloadditions to **2a** was

affected significantly by the substituent on the nitrone;[3b] in reactions with cyclic nitrones, *exo*-products were dominant.[3a]




**Scheme 2**

The regioselectivity of the cycloaddition is in accordance with the predictions of FMO theory and corresponds with our previous findings[3b] for cycloaddition of *C*-benzoyl-*N*-phenylnitrone with **2a**. In contrast to *C,N*-diphenylnitrones (HOMO dipole) where the nitrone oxygen atom selectively attacks the β-carbon of the α,β-unsaturated moiety of **2a**, *C*-benzoyl-*N*-phenyl- and *C*-ethoxycarbonyl-*N*-benzyl nitrone (LUMO dipole) also lead to formation of the second possible regioisomer.[3b]

Next we investigated optimization of the diastereoselectivity of this reaction by catalysis with Lewis acids and microwave irradiation. The addition of $MgBr_2.OEt_2$, $MgI_2$-$I_2$ and $ZnI_2$ as a Lewis acid has no beneficial effect; indeed no isoxazolidines **4a-6a** were formed, only starting nitrone **3** being completely recovered. When nitrone **3** reacts with lactone **2a** in the presence of Lewis acids, such as $TiCl_4$, $Ti(OiPr)_2Cl_2$ and $Ti(OiPr)_4$, very complicated inseparable mixtures of products are formed. Probably, in contrast to the successful Lewis acid catalyzed stereocontrol of 1,3-dipolar cycloaddition of nitrones to alkenes,[11] lactone **2a** does not contain moieties suitable for bidentate coordination.

Attempts to accelerate the cycloaddition by microwave irradiation were however successful (the reaction time decreased from hours to less than 10 min) with only a small change of stereoselectivity in favour of *exo*-**4** isomer (Table 1, entry 6).

**Table 1. 1,3-Dipolar cycloaddition of nitrone 3 with furanones 2a-f**

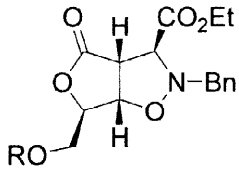
| Entry | Comp. | Solvent | r. temp. | 4 | 5 | 6 | *E/Z* |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | $CH_2Cl_2$ | 40°C | 30 | 56 | 14 | 1.5 |
| 2 | **2a** | MeOH | 65°C | 36 | 46 | 18 | 0.1 |
| 3 | **2a** | Benzene | 80°C | 53 | 37 | 10 | 3.7 |
| 4 | **2a** | DMSO | 80°C | 40 | 42 | 18 | 0.26 |
| 5 | **2a** | $Cl(CH_2)_2Cl$ | 80°C | 53 | 32 | 15 | - |
| 6 | **2a** | 1,4-Dioxane | MW[a] | 64 | 23 | 10[b] | - |
| 7 | **2b** | Benzene | 80°C | 64 | 25 | 11 | 3.7 |
| 8 | **2c** | Benzene | 80°C | 72 | 20 | 9 | 3.7 |
| 9 | **2d** | Benzene | 80°C | 78 | 17 | 5 | 3.7 |
| 10 | **2e** | Benzene | 80°C | 81 | 19 | - | 3.7 |
| 11 | **2f** | Benzene | 80°C | 83 | 15 | 2 | 3.7 |

[a]Microwave irradiation; [b]additionally 3 % of **8a**

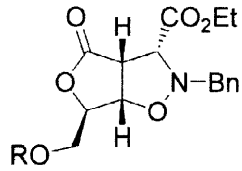
Moreover, in the case of microwave irradiation in dioxane a small amount of unexpected *syn* adduct **8a** (3 %) was also obtained after chromatography in addition to cycloadducts **4a-6a** (Table 1, entry 6). The $^1$H NMR spectrum of *syn*-**8a** could be assigned by COSY NMR data, and the stereochemistry again became apparent from NOE experiments. In particular, interactions were observed on the concave face of molecule between H-3a, H-6a and H-6. $^1$H NMR analysis also supports this structure since the isolated adduct **8a** showed $J_{6,6a}$ = 6.2 Hz, which is in the range expected for an H-6, H-6a *syn* relationship. Further support for this *syn* relationship may be drawn from the signal for H-6a appearing as a doublet of doublets.[7] The relative configuration between H-3 and H-3a is assigned from the absence of detectable coupling between than; the singlet signal for H-3 is consistent with an *anti* arrangement of these C-H bonds.

Finally, the cycloaddition in benzene of nitrone **3** with *O*-substituted lactones **2b-f**, where R is Ac, Bz, Pv, TBDMS (*t*-Bu$Me_2$Si) and TBDPS (*t*-Bu$Ph_2$Si) has been studied (Scheme 3). Each of **2b-f** reacts in boiling benzene in a highly face-stereoselective fashion to furnish a mixture of diastereomeric cycloadducts **4b-f**, **5b-f** and **6b-f**, from which the major *exo*-**4b-f** could be separated by flash chromatography. Structures of cycloadducts were assigned by analogy to **4a-6a**.

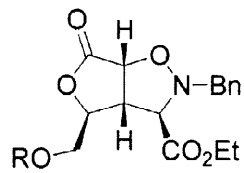
b R = Ac
c R = Bz
d R = Pv
e R = TBDMS
f R = TBDPS




4b-f




5b-f




6b-f

**Scheme 3**

The relative configuration of major *exo*-adducts **4b-f** is shown to parallel that observed for **4a** on the basis of the close agreement of the characteristic proton resonances and coupling patterns for this series of molecules. In each case only *anti*-cycloadducts **4-6** were formed, confirming the key assumption that the template alkoxymethyl group would effectively shield the upper face of the lactones **2b-f**. Diastereoselectivity of cycloadditions to *O*-substituted **2b-f** is dependent on the steric hindrance of lactone. The reaction compared to unsubstituted parent lactone **2a** proceeded more selectively in favour of *exo*-diastereoisomers **4b-f**, the selectivity increasing as the size of protected group attached to the lactone increases; 53 : 37 : 10 for R = H and 83 : 15 : 2 for R = TBDPS (Table 1, entries 3 and 11).

In conclusion, the cycloaddition of *N*-benzyl-*C*-ethoxycarbonyl nitrone (**3**) with (*S*)-5-hydroxymethyl-2(5*H*)-furanone (**2a**) and its 5-alkoxysubstituted derivatives **2b-f** proceeds smoothly in a highly face-selective manner, the products **4-6** resulting from approach *anti* to the hydroxymethyl and alkoxymethyl group of the dipolarophile, respectively. The *exo*-stereoselectivity increases as the size of protected group attached to the lactone increases.

## EXPERIMENTAL

*General.* $^{1}H$ NMR spectra were recorded at 300 MHz and $^{13}C$ NMR spectra at 75 MHz on a Varian VXR 300 spectrometer or at 500 MHz and 125 MHZ, respectively on a Bruker AC 500 spectrometer at 293 K in $CDCl_3$ solution, unless otherwise stated. Chemical shifts are reported in ppm ($\delta$) downfield from TMS and coupling constants (J) are given in Hz. Optical rotations were measured on a IBZ Messtechnik Polar - LμP instrument. Infrared spectra were measured on the Philips Analytical PU 9800 FTIR spectrometer. Elemental analyses were obtained on a EA 1108 - Elemental Analyzer (Carlo Erba) instrument. Melting points are

uncorrected. Commercial reagents were purified before use. Flash chromatography was carried out on 63-200 μm or 40-60 μm silica gel; thin layer chromatography was carried out on aluminium backed silica plates containing $UV_{254}$ by Lachema and plates are visualised with UV light and Mostaine solution, as appropriate.

Starting compounds - methyl and ethyl (*S*)-4,5-dihydroxy-4,5-*O*-isopropylidene-2-pentenoate,[12] (*S*)-(5)-acetoxy-2-penten-4-olide (**2b**),[12] (*S*)-(5)-benzoyloxy-2-penten-4-olide (**2c**),[16] (*S*)-(5)-tert-butyldimethylsilyloxy-2-penten-4-olide (**2e**)[12] and (*S*)-(5)-tert-butyldiphenylsilyloxy-2-penten-4-olide (**2f**)[17] were synthetisized by literature procedures. *C*-Ethoxycarbonyl-*N*-benzyl nitrone (**3**) was prepared from ethyl glyoxylate[13] and *N*-benzylhydroxylamine[14] according Dondoni[15] protocol.

**(*S*)-5-Hydroxy-2-pentene-4-olide (2a).** To a solution of 22.5 g (0.12 mol) of methyl (*S*)-4,5-dihydroxy-4,5-*O*-isopropylidene-2-pentenoate[12] in 50 ml methanol were added 1.5 ml of 30 % methanolic $H_2SO_4$ and 4.3 ml (0.24 mol) $H_2O$ and the mixture was stirred at the room temperature. After 2 h the mixture was neutralised by adding 0.25 M methanolic solution of NaOH to pH 6 under strong stirring, the solvent was evaporated to drynes *in vacuo* at room temperature. Dichloromethane (70 ml) and $Na_2SO_4$ (5g) were added to the residue, stirred for 30 min, filtered and evaporated *in vacuo*. Hot *i*-hexane was added, the mixture was stirred 5 min, cooled to 0°C in refrigerator giving colorless solid. This operation was repeated 3 times, and 11.8 g (85 %) of lactone **2a** was obtained. M.p. 41-43 °C, Lit.[12] 42-43 °C. $[\alpha]_D^{23} = -142$ (c = 1.21, $H_2O$; Lit.[12] $[\alpha]_D^{20} = -154.5$, c = 1.135, $H_2O$. All NMR data of **2a** found to be identical with those reported.[12]

**(*S*)-(5)-Pivaloyloxy-2-penten-4-olide (2d).** To a solution of 500.0 mg (4.38 mmol) lactone **2a** in 5 ml of dry $CH_2Cl_2$ 530.0 mg (4.40 mmol) of pivaloyl chloride and 347.0 mg (4.38 mmol) of pyridine were added at -10°C under stirring. The mixture was kept at 0°C for 24 h and than diluted with 15 ml of $CH_2Cl_2$, partitioned against 2 x 10 ml of 2 % $NaHCO_3$, 1 x 10 ml of water. The aqueous phase was reextracted (2 x 5 ml $CH_2Cl_2$), the extract was dried (5g $Na_2SO_4$) and concentrated. The crude product (830.0 mg, 95 %) was obtained, which was crystallized very slowly at room temperature. M.p. 28-32 °C ($CH_2Cl_2$). $[\alpha]_D^{23} = -129$ (c = 1.06, $CHCl_3$); IR spectrum (film): $\tilde{\nu}$ = 2977, 1763, 1732, 1482, 1283, 1157, 1111, 828 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, 500 MHz): δ 1.14 (9H, s, $C(CH_3)_3$), 4.35 (2H, d, $J^3$ = 4.1 Hz, $\underline{CH_2}O$), 5.22 (m, 1H, H-4), 6.17 (dd, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 2.0 Hz, 1H, H-3), 7.40 (dd, $J_{2,3}$ = 5.8 Hz, $J_{2,4}$ = 1.6 Hz, 1H, H-2); $^{13}C$ NMR (125 MHz): δ 26.98 (q, $C(\underline{CH_3})_3$, 38.81 (s, $\underline{C}(CH_3)_3$), 61.94 (t, C-5), 80.98 (d, C-4), 123.12 (d, C-2), 152.38 (d, C-3), 172.22 (s, CO), 177.96 (s, CO).

**Cycloadditon of nitrone 3 to lactone 2a.** To a solution of 830.0 mg (7.3 mmol) lactone **2a** in 20 ml of benzene was added 1500 mg (7.3 mmol) of nitrone (**3**) and the mixture was stirred and heated under reflux for 6 h. After reaction was complete (TLC monitoring) the mixture was cooled, the solvent evaporated and the residue purified by column chromatography (silica gel 60g, *i*-hexane - ethyl acetate 5 : 2, ∅ 2.5 cm) yielded isomers **4a – 6a.** **(*3S, 3aR, 6aS, 6R*)-Ethyl (2-benzyl-6-hydroxymethyl-4-oxotetrahydrofuro [3,4-d]**

**isoxazolidine-3-carboxylate) (4a).** Yield 710 mg (30 %). M.p. 80-81 °C (ethyl acetate - *i*-hexane); $[\alpha]_D^{25}$ = – 43.0 (c = 1.02, $CHCl_3$). For $C_{16}H_{19}NO_6$ MW. 321.3 calc. C 59.81 %, H 5.96 %, N 4.36 %; found C 59.56 %, H 6.16 %, N 4.51 %. $^1$H NMR (300 MHz): δ 1.28 (3H, t, J = 7.2 Hz, $OCH_2\underline{CH_3}$), 3.00 (1H, bs, OH), 3.70 (1H, dd, J = 2.4, 12.6 Hz, $\underline{CH_2}OH$), 3.87 (1H, dd, J = 2.7, 12.6 Hz, $\underline{CH_2}OH$), 3.89 (1H, d, $J_{3,3a}$ = 2.7 Hz, H-3), 3.95 (1H, dd, $J_{3,3a}$ = 2.7 Hz, $J_{3a,6a}$ = 6.6 Hz, H-3a), 4.15 (4H, m, J = 13.8, 7.2 and 7.2 Hz, $\underline{CH_2}Ph$, $O\underline{CH_2}CH_3$), 4.55 (1H, m, H-6), 4.78 (1H, d, $J_{3a,6a}$ = 6.6 Hz, H-6a), 7.29 (5H, m, H-arom); $^{13}$C NMR (75 MHz): δ 14.1 (q, $CH_3$), 53.1 (d, C-3a), 60.8 (t, $\underline{CH_2}Ph$), 62.1 (t, $O\underline{CH_2}CH_3$), 62.1 (t, $CH_2OH$), 69.4 (d, C-3), 80.1 (d, C-6a), 84.0 (d, C-6), 127.8, 128.4, 128.9, 136.1 (C-arom), 168.3 (s, C=O), 176.7 (s, C=O); **(*3R, 3aR, 6aS, 6R*)-Ethyl (2-benzyl-6-hydroxymethyl-4-oxotetrahydrofuro [3,4-d] isoxazolidine-3-carboxylate) (5a).** Yield 605 mg (26 %). M.p. 150-153 °C (chloroform - *i*-hexane); $[\alpha]_D^{25}$ = 123.0 (c = 0.51, $CHCl_3$). For $C_{16}H_{19}NO_6$ MW. 321.3 calc. C 59.81 %, H 5.96 %, N 4.36 %; found C 59.68 %, H 6.01 %, N 4.36 %. $^1$H NMR (300 MHz): δ 1.31 (3H, t, J = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.53 (1H, bs, OH), 3.68 (1H, d, $J_{3,3a}$ = 7.8 Hz, H-3), 3.70 (1H, dd, J = 2.6, 12.4 Hz, $\underline{CH_2}OH$), 3.78 (1H, dd, $J_{3,3a}$ = 7.8 Hz, $J_{3a,6a}$ = 7.5 Hz, H-3a), 3.85 (1H, d, J = 13.9 Hz, $\underline{CH_2}Ph$), 3.92 (1H, dd, J = 2.3, 12.4 Hz, $\underline{CH_2}OH$), 4.24 (3H, m, $O\underline{CH_2}CH_3$, $\underline{CH_2}Ph$), 4.58 (1H, d, $J_{6,6a}$ = 1.7 Hz, H-6), 4.86 (1H, dd, $J_{3a,6a}$ = 7.5 Hz, $J_{6,6a}$ = 1.7 Hz, H-6a), 7.30 (5H, m, H-arom); $^{13}$C NMR (75 MHz): δ 14.0 (q, $CH_3$), 52.2 (d, C-3a), 59.7 (t, $\underline{CH_2}Ph$), 61.8 (t, $O\underline{CH_2}CH_3$), 62.2 (t, $CH_2OH$), 69.1 (d, C-3), 78.0 (d, C-6a), 85.8 (d, C-6), 127.5, 128.5, 128.8, 135.3 (C-arom), 166.7 (s, C=O), 174.1 (s, C=O); **(*3R, 3aR, 4S, 6aR*) Ethyl-(2-benzyl-4-hydroxymethyl-6-oxotetrahydrofuro [4,3-d] isoxazolidine-3-carboxylate) (6a).** Yield 163 mg (7 %). M.p. 137-139 °C (chloroform - *i*-hexane); $[\alpha]_D^{25}$ = - 8.3 (c = 0.41, $CHCl_3$). For $C_{16}H_{19}NO_6$ MW. 321.3 calc. C 59.81 %, H 5.96 %, N 4.36 %; found C 59.54 %, H 6.25 %, N 4.44 %. $^1$H NMR (300 MHz): δ 1.31 (3H, t, J = 7.4 Hz, $OCH_2\underline{CH_3}$), 2.56 (1H, bs, OH), 3.64 (1H, ddd, $J_{3,3a}$ = 3.8 Hz, $J_{3a,4}$ = 1.8 Hz, $J_{3a,6a}$ = 8.2 Hz, H-3a), 3.67 (1H, dd, J = 12.3, 2.4 Hz, $\underline{CH_2}OH$), 3.91 (1H, dd, J = 12.3, 2.2 Hz, $\underline{CH_2}OH$), 3.97 (1H, d, H-3) 4.16 (2H, 2xd, J = 13.8 Hz, $\underline{CH_2}Ph$), 4.23 (2H, q, J = 7.4 Hz, $O\underline{CH_2}CH_3$), 4.61 (1H, m, H-4), 4.88 (1H, d, $J_{3a,6a}$ = 8.2 Hz, H-6a), 7.32 (5H, m, H-arom); $^{13}$C NMR (75 MHz): δ 14.2 (q, $CH_3$), 49.3 (d, C-3a), 58.8 (t, $\underline{CH_2}Ph$), 61.9 (t, $O\underline{CH_2}CH_3$), 63.4 (t, $CH_2OH$), 70.7 (d, C-3), 76.9 (d, C-4), 82.5 (d, C-6a), 127.8, 128.4, 128.9, 135.5 (C-arom), 168.3 (s, CO), 174.0 (s, CO).

**Cycloaddition of nitrone 3 to lactone 2a in dioxane.** Lactone **2a** (1.1g, 9.6 mmol) was dissolved in dioxane (20 ml) and nitrone **3** (2.0g, 9.6 mmol) was added and the mixture was irradiated carefully in the domestic microwave oven in a 100 ml open Erlenmayer flask for 10 x 1 min. at 350 W. The crude material was purified by flash chromatography (*i*-hexane - ethyl acetate 5 : 2), giving pure adducts **4a** (64 %), **5a** (23 %), **6a** (10 %) and **8a** (3%). **(*3R, 3aS, 6aR, 6R*)-Ethyl (2-benzyl-6-hydroxymethyl-4-oxotetrahydrofuro [ 3,4-d] izoxazolidine-3-carboxylate) (8a).** Yield 71 mg (3 %). M.p. 180-182 °C (chloroform - diethylether). For $C_{16}H_{19}NO_6$ MW. 321.3 calc. C 59.81 %, H 5.96 %, N 4.36 %; found C 59.55 %, H 6.08 %, N 4.49 %. $^1$H NMR (300 MHz): δ 1.33 (3H, t, J = 7.2 Hz, $OCH_2\underline{CH_3}$), 2.10 (1H, bs, OH), 3.67 (1H, d, $J_{3a,6a}$ = 7.2 Hz, H-3a), 3.76 (2 H, dd, J = 12.3, 5.6 Hz, $\underline{CH_2}OH$), 3.77 (1H, d, J = 13.6 Hz, $CH_2Ph$), 3.82 (1H, s, H-3), 3.83 (2H, dd, J = 2.6,

12.4 Hz, $\underline{CH_2}OH$), 4.28 (2H, q, J = 7.2 Hz, $O\underline{CH_2}CH_3$), 4.31 (1H, d, J = 13.6 Hz, $CH_2Ph$), 4.62 (1H, ddd, $J_{6,6a}$ = 6.2 Hz, H-6), 4.96 (1H, dd, $J_{3a,6a}$ = 7.2 Hz, $J_{6,6a}$ = 6.2 Hz, H-6a), 7.35 (5H, m, H-arom); $^{13}C$ NMR (75 MHz): δ 14.0 (q, $CH_3$), 51.5 (d, C-3a), 60.0 (t, $\underline{CH_2}Ph$), 60.4 (t, $O\underline{CH_2}CH_3$), 62.0 (t, $CH_2OH$), 69.2 (d, C-3), 76.3 (d, C-6a), 82.2 (d, C-6), 128.1, 128.5, 129.4, 135.1 (C-arom), 166.2 (s, C=O), 172.7 (s, C=O).

**Cycloadditon of nitrone 3 to lactone 2d.** To a solution of 198.2 mg (10.0 mmol) of lactone **2d** in 15 ml of benzene was added 207.2 mg (10.0 mmol) of nitrone **3** and stirred mixture was heated under reflux for 20 h. After finishing of reaction (TLC monitoring) was the mixture cooled, the solvent evaporated and the rest purified by flash chromatography (silica gel 40g, *i*-hexane - ethyl acetate 3 : 1, ∅ 1.8 cm) yielded 200 mg (49 %) of **(*3S, 3aR, 6aS, 6R*)-Ethyl (2-benzyl-6-pivaloyloxymethyl-4-oxotetrahydrofuro[3,4-d]isoxazolidine-3-carboxylate (4d)** as a yellow oil. $^1H$ NMR (300 MHz, acetone-$d_6$): δ 1.21 (9H, s, $C(\underline{CH_3})_3$ ), 1.34 (3H, t, J = 7.2 Hz, $OCH_2\underline{CH_3}$), 3.98 (1H, bs, H-3), 4.08 (1H, dd, $J_{3,3a}$ = 2.7 Hz, $J_{3a,6a}$ = 6.6 Hz, H-3a), 4.12 (1H, d, J = 13.8 Hz, $CH_2Ph$), 4.22 (1H, d, J = 13.8 Hz, $CH_2Ph$), 4.25 (2H, q, J = 7.2 Hz, $O\underline{CH_2}CH_3$), 4.38 (1H, dd, J = 3.3, 12.1 Hz, $\underline{CH_2}O$-), 4.40 (1H, dd, J = 3.3, 12.1 Hz, $\underline{CH_2}O$-) 4.81 (1H, m, H-6), 4.84 (1H, d, $J_{3a,6a}$ = 6.6 Hz, H-6a), 7.55 (5H, m, H-arom); $^{13}C$ NMR (75 MHz, acetone-$d_6$): δ 14.4 (q, $CH_3$), 27.4 (q, $C(\underline{CH_3})_3$), 39.3 (s, $\underline{C}(CH_3)_3$), 53.3 (d, C-3a), 60.8 (t, $\underline{CH_2}Ph$), 62.4 (t, $O\underline{CH_2}CH_3$), 64.8 (t, $CH_2OH$), 70.4 (d, C-3), 80.4 (d, C-6a), 81.9 (d, C-6), 128.2, 129.0, 129.6, 138.0 (C-arom), 168.7, 176.1, 177.8 (s, C=O). The other fractions gave 150 mg (37 %) of inseparable mixture isoxazolidines **5d** and **6d**.

**Cycloadditon of nitrone 3 to lactone 2e.** To a solution of 850.0 mg (37.2 mmol) of lactone **2e** in 25 ml of benzene was added 770.0 mg (37.2 mmol) of nitrone **3** and the mixture was stirred and heated under reflux for 20 h. After finishing of reaction (TLC monitoring) the mixture was cooled, the solvent evaporated and the residue purified by flash chromatography (silica gel 40g, *i*-hexane - ethyl acetate 3 : 1, ∅ 1.8 cm) yielded 680 mg (42 %) of **(*3S, 3aR, 6aS, 6R*) ethyl-(2-benzyl-6-tertbutyldimethylsilyloxymethyl-4-oxotetrahydrofuro [3,4d]isoxazolidine-3-carboxylate (4e)** as a yellow oil. $^1H$ NMR (300 MHz): δ 0.02 (6H, s, -$C(\underline{CH_3})_2$), 0.82 (9H, s, $C(\underline{CH_3})_3$), 1.20 (3H, t, J = 7.2 Hz, $OCH_2\underline{CH_3}$), 3.63 (1H, dd, J = 2.1, 11.1 Hz, $\underline{CH_2}O$-), 3.75 (1H, dd, J = 2.1, 11.1 Hz, $\underline{CH_2}O$-) 3.78 (1H, bs, H-3), 3.84 (1H, dd, $J_{3,3a}$ = 2.3 Hz, $J_{3a,6a}$ = 6.3 Hz, H-3a), 3.97 (1H, d, J = 13.8 Hz, $CH_2Ph$), 4.12 (3H, m, J = 7.2 Hz, 13.8 Hz, $O\underline{CH_2}CH_3$, $CH_2Ph$), 4.44 (1H, m, H-6), 4.65 (1H, d, $J_{3a,6a}$ = 6.3 Hz, H-6a), 7.29 (5H, m, H-arom); $^{13}C$ NMR (75 MHz): δ -6.1 (q, $(CH_3)_2$), 14.6 (q, $CH_3$), 17.6 (s, $\underline{C}(CH_3)_3$), 25.3 (q, $C(\underline{CH_3})_3$), 52.6 (d, C-3a), 60.5 (t, $\underline{CH_2}Ph$), 61.4 (t, $CH_2O$), 62.7 (t, $O\underline{CH_2}CH_3$), 69.1 (d, C-3), 80.0 (d, C-6a), 82.5 (d, C-6), 127.2, 127.9, 128.4, 136.0 (C-arom), 167.7, 175.6 (s, C=O). The other fractions gave 470 mg (29 %) of inseparable mixture isoxazolidines **5e** and **6e**.

**Dipolar cycloadditon of nitrone 3 to lactone 2f.** To a solution of 1.70 g (48.3 mmol) of lactone **2f** in 25 ml of benzene was added 1.0 g (48.3 mmol) of nitrone **3** and the mixture was stirred and heated under reflux for 36 h. After finishing of reaction (TLC monitoring) the mixture was cooled, the solvent evaporated and the

residue purified by column chromatography (silica gel 80g, *i*-hexane - dichlorometane 3 : 2, ∅ 3.5 cm) yielded 1.65 g (60 %) of **(3*S*, 3a*R*, 6a*S*, 6*R*)-ethyl (2-benzyl-6-tertbutyldiphenylsilyloxymethyl-4-oxotetrahydrofuro [3,4d]isoxazolidine-3-carboxylate (4f)** as a colourless oil. $^1$H NMR (300 MHz): δ 1.04 (9H, s, C($\underline{CH_3}$)$_3$), 1.31 (3H, t, J = 7.4 Hz, OCH$_2\underline{CH_3}$), 3.72 (1H, dd, J = 1.5, 11.7 Hz, $\underline{CH_2}$O-), 3.89 (1H, dd, J = 1.5, 11.7 Hz, $\underline{CH_2}$O-), 3.95 (1H, bs, H-3), 4.10 (3H, m, J = 13.8 Hz, $CH_2$Ph, H-3a), 4.24 (3H, m, J = 7.4, 13.8 Hz, $\underline{OCH_2}CH_3$, $CH_2$Ph), 4.56 (1H, m, H-6), 4.89 (1H, d, $J_{3a,6a}$ = 6.3 Hz, H-6a), 7.20-7.60 (15H, m, H-arom); $^{13}$C NMR (75 MHz): δ 14.1 (q, $CH_3$), 19.1 (s, $\underline{C}(CH_3)_3$), 26.7 (q, C($\underline{C}H_3$)$_3$), 53.2 (d, C-3a), 61.0 (t, $\underline{CH_2}$Ph), 62.1 (t, $CH_2$O), 63.7 (t, O$\underline{CH_2}CH_3$), 69.6 (d, C-3), 80.5 (d, C-6a), 83.3 (d, C-6), 127.7, 127.8, 128.0, 128.4, 128.9, 129.6, 130.1, 130.1, 131.7, 132.2, 134.8, 135.5, 135.6, 136.0 (C-arom), 168.1, 176.1, (s, C=O).

**Acknowledgements.**

The authors are grateful to the Slovak Grant Agency (No. I/4210/97 and No. 95/195/202) and Volkswagen Stiftung for financial support. The authors thank Professor V. Jäger and Dr. Lieberknecht, Stuttgart, for helpful discussions.

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