1,3-Dipolar cycloadditions of mesitonitrile oxide to chiral α,β-unsaturated enones catalyzed by Lewis acids

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Dedicated to Professor Ľubor Fišera on the occasion of his 60th birthday

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Abstract

The influence of $MgBr_2$, MgI_2 and $Ti(OiPr)_4$ on the regio- and stereoselective outcome of 1,3-dipolar cycloaddition of mesitonitriloxide **1** to both *E and Z* isomers of (5*S*)-5,6-(*O*-isopropylidenedioxa)hex-3-en-2-one (**2a**) or (4*S*)-1-(2-furyl)-4,5-(*O* isopropylidenedioxa) pent-3-en-1-one (**2b)** was studied. Addition of Lewis acids in some cases has a dramatic effect on the regiochemistry as well as on the diastereomeric ratio of cycloadducts.

Keywords: Metal assisted 1,3-dipolar cycloaddition, α,β-unsaturated enones, regio- and diastereoselection, isoxazolines

Introduction

The development of 1,3-dipolar cycloaddition reactions has in recent years entered a new stage as control of the stereochemistry in the addition step became the major challenge. The stereochemistry of 1,3-dipolar cycloaddition reactions can be controlled by either choosing the appropriate substrates or controlling the reaction by a metal complex acting as a catalyst. The papers dealing with successful examples of metal-catalyzed or metal-assisted 1,3-dipolar cycloadditions are not still very numerous.[1-5]

An impressive effort has been devoted to the synthetic application of 1,3-dipolar cycloaddition of nitrile oxides.[6,7] One of the key features of those processes resides in the *cis*-stereospecificity of the cycloaddition, that transfers the stereochemical information of the alkene to the stereocentres of the heterocyclic ring.[6-8] Thus, from *E* alkenes 4,5-*anti* products are obtained, while *Z* alkenes afford *4,5*-syn compounds. A large part of the research in this area dealt with the influence exerted by stereocentre located in either one of the two cycloaddends, with the stereochemical outcome of the reaction. The low degree of stereoselection generally

showed by the cycloaddition of chiral nitrile oxides promoted an intense research activity on the use of chiral alkenes as dipolarophiles. The basic factors governing the stereochemical course of these reactions are summarized in research work of R. Annunziata and coworkers.[9]

The regioselectivity phenomena are a case of competition between two different modes of union of unsymetrical reactants, hence the electronic and steric effects on reactivity have to be confronted. The nitrile oxides cycloadditions to terminal alkenes proceed rapidly and with complete regioselectivity to yield only 5-substituted isoxazolines as unique products.[6] On the other hand, reactions of nitrile oxides with 1,2-disubstituted internal alkenes are sluggish and mostly mixture of regioisomeric isoxazolines are formed. [7,8] The use of alkenes with chiral center arises as well the problem of diastereoselectivity, which is generally not very high and depends mainly upon the nature of both the dipole as well as the dipolarophile. When 1,3-dipolar cycloaddition is to be used in any synthesis of a complex target molecule, a method that accomodates change or even reversal of the regio- or diastereoselectivity would be desirable. Recently, 1,3-dipolar cycloadditions of chiral α,β-unsaturated enones of glyceraldehyde type with azomethine ylides,[10,11] diazo-compounds,[12] nitronates[13] and nitrilimines[14] were described. Based on this facts we decided to investigate stereochemical behavior the cycloadditions of mesitonitrile oxide (**1**) with *E* and *Z* isomers of enones (5*S*)-5,6- (*O*-isopropylidenedioxa)hex-3-en-2-one (**2a**) and (4*S*)-1-(2-furyl)-4,5-(*O*-isopropylidenedioxa)pent-3-en-1-one (**2b**), as well as the influence of some Lewis acids ($MgBr_2$, MgI_2, $Ti(OiPr)_4$) on regio- and stereochemical outcome of these 1,3-dipolar cycloadditions.

Results and Discussion

The mesitonitrile oxide (**1**) was chosen for afore mentioned cycloadditions as one of the most stable nitrile oxide with minimum side reactions and the enones *Z*-**2a** , *E*-**2a**[15a,b] and *Z*- **2b,** *E*-**2b** (firstly prepared by us) as electron deficient dipolarophiles. The enones were prepared by general Wittig methodology previously described in the literature for the variety similar enones.[16-18] As a starting material was used (*R*)-2,3-(*O*-isopropylidene) glyceraldehyde (**3**) prepared from commercially available 1,2:5,6-di(*O*-isopropylidene)-D-manitol by oxidative cleavage with sodium metaperiodate.[19] As we would like to obtain both isomers (*E* and *Z*) the Wittig reaction was realized in polar solvent (methanol) and at the lower temperature (from 0 to -15°C). The enones *E*-**2a** and *Z*-**2a** were obtained in the ratio 60:40 in two steps with overall yield 58%. The enones *E*-**2b** and *Z*-**2b** were prepared in four steps starting from 2-(bromoacetyl)furane[20] *via* particular phosphonium bromide to the corresponding ylide, which by Wittig reaction with chiral (*R*)-2,3-(*O*-isopropylidene)glyceraldehyde afforded enones **2b**, as a mixture of *E* and *Z* isomers (65 : 35) in overall yield 42%. The pure *E* and *Z* isomers were isolated by chromatography on silica gel using *iso*hexane/ethyl acetate (5:1) as eluent.

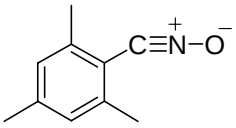
The 1,3-dipolar cycloaddition reactions were firstly carried in absence of any catalyst, afterwards $MgBr_2$, MgI_2 or $Ti(OiPr)_4$ were used as catalyst. Change of solvent or alteration of

reaction temperature had only slight influence on the regio- and diastereoselectivity of the reaction. The results and reaction conditions of all experiments are summarized in Table 1. Ratio of regioisomers, as well as the relative configuration of the substituted isoxazolines (Scheme 1) were elucidated by various NMR methods. The ratio of regioisomers have been determined by integration of regioisomeric adducts in the ^{1}H NMR spectra of crude reaction mixtures and corresponds closely to those obtained by the chromatographic separations. All noncatalyzed cycloadditions of mesitonitrile oxide and enones *E*-**2a**, *Z*-**2a** and *E*-**2b** gave the mixture of both regioisomers with prevailing cycloadduct 4-acyl substituted isoxazolines, characterized by C-5/C-6 *anti* relationship (Table 1, entries 1, 5, 6, 16, 17). The enone *Z*-**2b** gave as a main products the second possible regioisomer (5-acylsubstituted isoxazolines) with totally opposite C-4/C-6 *syn* configuration (entries 11 and 12). In the cycloadditions of enones *E*-**2a**, *Z*-**2a** and **2b** under catalysis no or only a slight change of regio- and diastereoselectivity was observed (entries 2, 7, 8, 18). In accordance with obtained experimental results we suppose that both, catalyzed and noncatalyzed cycloadditions of afore mentioned enones could be characterized by the similar transition states (Scheme 2, model B and chelated model). In the case of *Z* isomers chelated 7-membered metalocycle can be formed through the chelatation of Mg^{2+}ion and two oxygen atoms and this transition state corresponds to the model B (Scheme 2), where the selectivity of the cycloaddition is determined by the influence of the „inside alkoxy" effect (Scheme 2, attack 1). Therefore predominantly 4-acyl C-5/C-6 *anti* isoxazolines **4a** and **4b** are formed (Table1, entries 2,7,8).

Table 1. 1,3-Dipolar cycloadditions of mesitylnitrile oxide **1** with chiral enones *Z*-**2a** and *Z*-**2b**

	Dipolarophile	Solvent	R.temp. [^{o}C]	React.time [hours]	Catalyst	Ratio of **4 : 5 : 6 : 7**
1	(*Z*) CH_3	1,4-dioxane	104	5	-	44 : 11 : 42 : 3
2	(*Z*) CH_3	THF	67	100	$MgBr_2$.THF	56 : 19 : 25 : [a]
3	(*Z*) CH_3	THF	67	100	MgI_2-I_2	[b]
4	(*Z*) CH_3	THF	67	100	$Ti(OiPr)_4$	-
5	(*Z*) 2-furyl	1,4-dioxane	104	3	-	2 : 3 : 32 : 63
6	(*Z*) 2-furyl	THF	67	100	-	14 : 6 : 32 : 48
7	(*Z*) 2-furyl	THF	67	100	$MgBr_2$.THF	55 : 22 : 23 : -
8	(*Z*) 2-furyl	THF	67	100	MgI_2-I_2	78 : 22 : - : -
9	(*Z*) 2-furyl	THF	67	100	$Ti(OiPr)_4$	-

[a] Not detected in crude reaction mixture (^{1}H NMR). [b] only (*R*)-4-acetyl-5-[(6,7-*O*-isopropylidene)-6,7-dihydroxyetyl]-3-mesitylisoxazole (**12**) was isolated.



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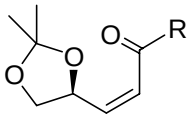
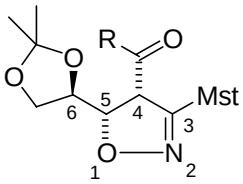
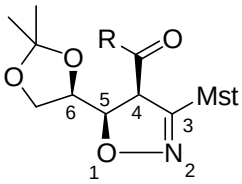


***Z*-2a,b**

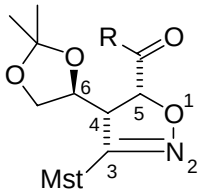
2a R = CH_3
2b R = 2-furyl



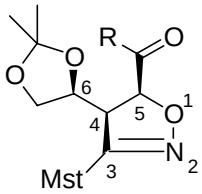
5,6-anti
4a,b



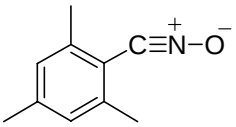
5,6-syn
5a,b



4,6-anti
6a,b



4,6-syn
7a,b



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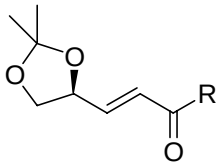
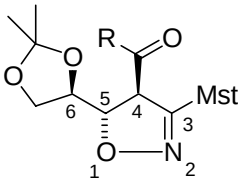
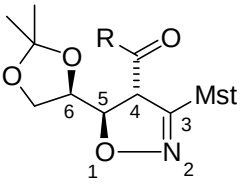


***E*-2a,b**

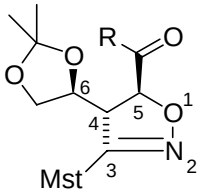
2a R = CH_3
2b R = 2-furyl



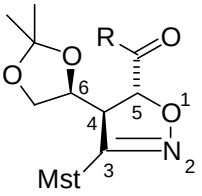
5,6-anti
8a,b



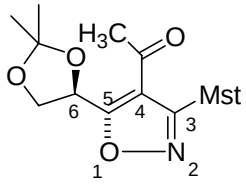
5,6-syn
9a,b



4,6-anti
10a,b



4,6-syn
11a,b



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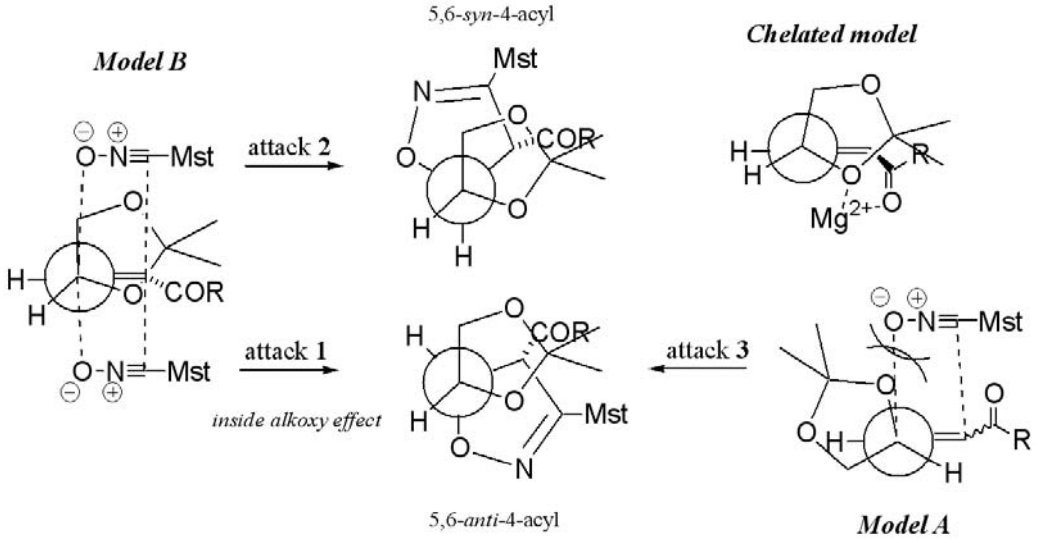
Scheme 1

The use of MgI2 most probably inhibited the cycloaddition of enones Z-2a and E-2a, so only the traces of the cycloadducts could be identified (Table 1, entry 3, Table 2, entry 5). In the case of enone Z-2a 4-acyl-3,5-disubstituted isoxazole 12 was isolated from reaction mixture in 13% yield, the rest of reaction mixture was the non-identified tars.

Table 2. 1,3-Dipolar cycloadditions of mesitylnitrile oxide **1** with chiral enones *E*-**2a** and *E*-**2b**

	Dipolarophile	Solvent	R.temp. [°C]	React.time [hours]	Catalyst	Ratio of **8 : 9 : 10 : 11**
1	(*E*) CH_3	1,4-dioxane	104	5	-	50 : 14 : 32 : 4
2	(*E*) CH_3	Et_2O	35	24	-	48 : 10 : 37 : 5
3	(*E*) CH_3	Et_2O/methanol	35	100	$MgBr_2$.THF	46 : 8 : 46 : -
4	(*E*) CH_3	THF	67	100	$MgBr_2$.THF	50 : 13 : 37 : -
5	(*E*) CH_3	THF	67	100	MgI_2-I_2	c
6	(*E*) CH_3	THF	67	100	$Ti(OiPr)_4$	-
7	(*E*) 2-furyl	1,4-dioxane	104	3	-	54 : 18 : 28 : -
8	(*E*) 2-furyl	THF	67	12	-	36 : 29 : 35 : -
9	(*E*) 2-furyl	THF	67	100	$MgBr_2$.THF	59 : 16 : 25 : -
10	(*E*) 2-furyl	THF	67	100	MgI_2-I_2	75 : 21 : 4 : -
11	(*E*) 2-furyl	THF	67	100	$Ti(OiPr)_4$	-

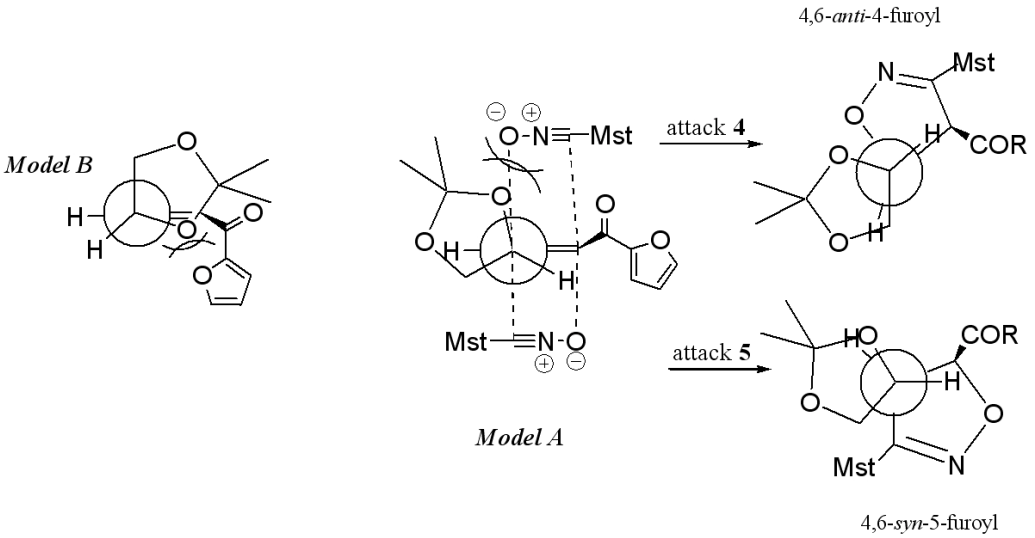
[c] Only traces of cycloadduct were detected in crude reaction mixture.



Scheme 2

More interesting results were obtained in cycloadditions of both enones *E*-**2b** and *Z*-**2b** to mesitonitrile oxide (**1**) under catalysis with magnesium halogenides. Apart from stereochemical outcome the cycloaddition of *E*-**2b** in the presence of $MgBr_2$ where only very slight growth of

cycloaduct **8b** was observed (Table 2, entry 9), in other cases both magnesium halogenides significantly improved regio- and diastereoselectivity. In the case of enone *Z*-**2b**, total reversal of regiochemistry occured, together with the change of diastereoselectivity (Table 1, entries 7, 8) and 4-furoylsubstituted isoxazolines **4b** and **5b** were formed as a main product with preponderance of C-5/C-6 *anti* relationship.The same dramatic improvement of regio- and stereoselectivity has been observed in cycloaddition reactions of enone *E*-**2b** under catalysis with MgI_2-I_2 (Table 2, entry10). The complete reversal of regiochemistry of *Z*-**2b** in cycloadditions can be rationalized by different transition state of noncatalyzed and catalyzed cycloaddition (with different geometry). The electronic repulsion between nitrile oxide oxygen and oxygen atom of the alkoxy group, together with the bulky 2-furoyl group inhibits the cycloaddition through the *Model B* (Scheme 3, attack 4) and so predominantly 5-furoyl C-4/C-6 *syn* and 5-furoyl C-4/C-6 *anti* isoxazolines **7b** and **6b** are formed through *Model A* (Scheme 3, attack 5). The chelatation of *Z*-**2b** with Mg^{2+}ions prefer the cycloaddition through the Model B (Scheme 2, chelated model, R= 2-furoyl) generating 4-furoylsubstituted 5/6 *anti* isoxazolines (Table 1, entries 7, 8).



Scheme 3

The use of titanium(tetra*iso*propoxy) as catalyst in 1,3-dipolar cycloaddition of enones **2** and nitriloxide **1** totally failed.

The products of cycloadditions were isolated by flash column chromatography on silica gel and the pure diastereomers are characterized by characteristic physical constants and *via* analysis their ^{1}H NMR and ^{13}C NMR spectral data. The ratio of isomers was determined from ^{1}H NMR spectra, by integration of the peaks from H-4 a H-5 protons of isoxazolines. The structures and stereochemistries of prepared cycloadducts were eluciated on the base of ^{1}H and ^{13}C NMR spectra, using the selective decapling, heterocorelated 2D spectra and n.O.e difference experiments. All ^{1}H NMR characteristics of proton H-4, H-5 and H-6 are summarized in the Table 3.

Table 3. Multiplicity, chemical shifts and interaction constants of protons H-4, H-5 and H-6

Comp. No.	H-4 δ/ppm	H-5 δ/ppm	H-6 δ/ppm	$J_{4,5}$/Hz	$J_{4,6}$/Hz	$J_{5,6}$/Hz
4a	d 4.59	dd 5.11	ddd 4.23	7. 40	—	7.40
5a	d 4.66	dd 5.25	ddd 4.29	8.0	—	2.80
6a	dd 4.15	d 4.99	ddd 4.23	11.80	5.0	—
8a	d 4.59	dd 5.11	ddd 4.23	7.14	—	6.95
9a	d 4.65	dd 5.25	ddd 4.28	7.97	—	2.75
10a	dd 3.84	d 5.03	ddd 4.13	4.9	4.1	—
11a	dd 3.64	d 4.94	ddd 4.15	5.5	6.3	—
4b	d 5.22	dd 5.23	ddd 4. 35	10.40	—	6.90
5b	d 5.30	dd 5.37	ddd 4. 37	7.70	—	2.75
6b	dd 4.18	d 5.63	ddd 4.34	10.70	7.40	—
7b	dd 4.95	d 5.62	ddd 4.40	10.90	9.30	—
8b	d 5.22	dd 5.24	ddd 4.35	5.20	—	6.90
9b	d 5.30	dd 5.37	ddd 4.37	7.69	—	2.75
10b	dd 4.20	d 5.64	ddd 4.26	5.49	4.40	—

The chemical shifts and spin multiplicity of protons H-4 and H-5 of isoxazoline ring obtained from ^{1}H NMR spectra were the decisive informations for the structural assigments of both regioisomers (4-acyl or 5-acyl). The stereochemistry of the cycloadducts was identifioed by spectroscopic analysis, particularly by n.O.e. difference experiments.

In conclusion, use of MgX_2 halogenides in 1,3-dipolar cycloadditions of mesitonitrile oxide to chiral α,β-unsaturated enones (using both *E* and *Z* isomers) improved the regio- and stereoselective outcome of those reactions. Predominantly 4-acylsubstituted C-5/C-6 *anti* isoxazolines were formed. In one case (enone *Z*-**2b**) the addition of catalyst caused the total reversal of regiochemistry and stereochemistry.

Experimental Part

General Procedures. All melting points were determined with a Kofler hot-stage apparatus, the IR spectra were taken with-Philips analytical PU 9800 FTIR spectrometer in KBr pellets, the ^{1}H and ^{13}C NMR spectra were recorded on Varian VXR-300 and Varian Gemini 2000 spectrometer (^{1}H 300 MHz, ^{13}C 75 MHz) in deuterochloroform solutions. Chemical shifts are expressed in ppm from internal standard (tetramethylsilane, δ) and coupling constants are in hertz (Hz). TLC analyses were carried out with UV 254 silica gel plates (Merck). Flash chromatography was done on silica gel 60 (0.040-0.063 mm, Merck). Optical rotations $[\alpha]_D$ were measured on IBZ Messtechnik Polar-LμP polarimeter at the sodium D line (589 nm) using a 1 dm cell at 25 °C in methanol. Elemental analyses were caried out on Carlo Erba CHNS-O 1108 apparatus and their results were found to be in good agreement with calculated values.

Mesitonitrile oxide (**1**) was prepared according to literature.[21] Reagents $MgBr_2$ and MgI_2 were freshly prepared prior to use, tetraisopropoxytitane is comercially available (Merck). (*R*)-2,3-(*O*-Isopropylidene)glyceraldehyde was prepared from 1,2:5,6-di(*O*-isopropylidene)-D-manitol by oxidative cleavage with $NaIO_4$.[19] Starting enones (*S*)-5,6-(O-isopropylidene)hex-3-ene-2-one (*Z*-**2a** and *E*-**2a)** were prepared similarly to literature[15b](using different solvent and reaction temperature). The yields in experimental part are given for isolated cycloadducts after column chromatography. The ratio of regio- and diastereomers was determined from NMR spectra of crude reaction mixtures.

(*E* and *Z*)-(*S*)-1-(2-Furyl)-4,5-dihydroxy-4,5-(*O*-isopropylidene)pent-2-en-1-one (2b). To the solution of (*R*)-2,3-(*O*-isopropylidene)glyceraldehyde (1.95 g, 15 mmol) in dry methanol (30 ml) was added under stirring (2-furoyl)-methylidenetriphenyl-phosforane (6.66 g, 18 mmol) at – 15 °C. Reaction mixture was stirred for 12 h at the temperature below 0 °C and the following 12 h at room temperature (monitored by TLC (hexanes/ethyl acetate, 75:25). The solvent was removed by rotary evaporation and the pure isomers *E*-**2b** *Z*-**2b** were separated by flash column chromatography on silica (hexanes/ethyl acetate, 80:20) as a colourless solids in a ratio *E:Z* 65:35, in overall yield 1.4 g (42 %).

(*Z*)-(*S*)-1-(2-Furyl)-4,5-dihydroxy-4,5-(*O*-isopropylidene)pent-2-en-1-one (*Z*-2b). Colourless solid, R_f = 0.36 (hexanes/EtOAc, 75:25), mp 47-49 °C, $[\alpha]_D$ = +47.27 (*c* 0.11);); for $C_{12}H_{14}O_4$ (Mw 222.24) w_i(calc.): 64.85% C, 6.35% H; w_i(found): 64.58% C, 6.54% H; IR (ν/cm^{-1}): 3133 (H-C= furan), 2988 (H-C=), 2937, 2890 (H-C), 1655(CO); ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.41 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.67 (dd, 1H, H-5b, $J_{4,5b}$ = 6.7 Hz, $J_{5a,5b}$ = 8.3 Hz), 4.53 (dd, 1H, H-5a, $J_{4,5a}$ = 7.8 Hz), 5.51 (ddd, 1H, H-4, $J_{3,4}$ = 6.3 Hz, $J_{2,4}$ = 1.75 Hz), 6.51 (dd, 1H, H-3, $J_{2,3}$ = 11.6 Hz), 6.57 (dd, 1H, H-4′, $J_{3',4'}$ = 3.5 Hz, $J_{4',5'}$ = 1.4 Hz), 6.83 (dd, 1H, H-2), 7.23 (d, 1H, H-3′), 7.64 (d, 1H, H-5′); ^{13}C NMR (75 MHz; $CDCl_3$) δ/ppm: 25.3 (CH_3), 26.6 (CH_3), 69.7 (C-5), 74.6 (C-4), 109.7 [$C(CH_3)_2$], 112.6 (C-4′), 117.9 (C-3′), 123.2 (C -2), 146.9 (C-3), 150.2 (C-5′), 178.4 (CO).

(*E*)-(*S*)-1-(2-Furyl)-4,5-dihydroxy-4,5-(*O*-isopropylidene)pent)-2-en-1-one (*E*-2b). Colourless solid, R_f = 0.27 (hexanes/EtOAc, 70:30), mp 27-28 °C, $[\alpha]_D$ = +3.14 (*c* 0.13);); for $C_{12}H_{14}O_4$ (Mw 222.24) w_i(calc.): 64.85% C, 6.35% H; w_i(found): 64.96% C, 6.63% H;
IR (ν/cm^{-1}): 3127(H-C= furan), 2991(H-C=), 2938, 2876(H-C), 1669(CO); ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.46 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 3.73 (dd, 1H, H-5b, $J_{4,5b}$ = 7.0 Hz, $J_{5a,5b}$ = 8.3 Hz), 4.24 (dd, 1H, H-5a, $J_{4,5a}$ = 6.9 Hz), 4.79 (ddd, 1H, H-4, $J_{3,4}$ = 3.2 Hz), 6.58 (dd, 1H, H-4′, $J_{3',4'}$ = 3.6 Hz, $J_{4',5'}$ = 1.4 Hz), 7.07 (d, 2H, H-2, H-3, $J_{2,3}$ = 18 Hz), 7.30 (d, 1H, H-3′), 7.66 (d, 1H, H-5′); ^{13}C NMR δ/ppm: 25.7 (CH_3), 26.4 (CH_3), 68.8 (C-5), 75.3 (C-4), 110.2 [$C(CH_3)_2$], 112.5 (C-4′), 118.4 (C-3′), 125.0 (C -2), 144.0 (C-3), 147.0 (C-5′), 153.0 (C-2′), 177.5 (CO)

1,3-Dipolar cycloadditions of mesitonitrile oxide (1) with the enone 2. General procedure, without catalyst

Mesitonitrile oxide (**1**, 1 mmol) and corresponding enone (1 mmol) dissolved in 10 ml of dry solvent (the appropriate solvent, reaction time and temperature are listed in Table 1 and Table 2) were stirred under reflux until complete conversion of nitrile oxide **1** (monitored by TLC). The solvent was evaporated under vacuum and the products were isolated by flash column chromatography on silica (hexanes/ethyl acetate).

General procedure, with $MgBr_2$ or MgI_2 as catalyst. The reactions were carried out under argon atmosphere. To the stirred solution of $MgBr_2$ or MgI_2 (1 mmol) in dry solvent (6 ml), was added the solution of mesitonitrile oxide (**1**, 1 mmol) in dry solvent (2 ml) by portions and the mixture was stirred 15 min at room temperature. The solution of corresponding enone (1 mmol) in dry solvent (2 ml) was added dropwise and reaction mixture was stirred under reflux (monitored by TLC). The solvent was removed under vacuum and if $MgBr_2$ was used as catalyst, the residue was diluted with CH_2Cl_2 (10 ml), the solid was filtered off and solvent removed by rotary evaporation; in the case of MgI_2, the residue was diluted with CH_2Cl_2 (10 ml), washed twice with 10% solution of $Na_2S_2O_3$ to remove I_2, dried over Na_2SO_4 and the solvent was removed under vacuum. The products were isolated by flash column chromatography on silica (hexanes/ethyl acetate).

General procedure, with (*i*-PrO)$_4$Ti as catalyst. The reactions were carried out under argon atmosphere. To the stirred solution of (*i*-PrO)$_4$Ti (1 mmol) in dry THF (6 ml) was added solution of mesitonitrile oxide (**1**, 1mmol) in dry THF (3 ml) by portions and the mixture was stirred 15 min at room temperature. The solution of corresponding enone (1 mmol) in dry THF (3 ml) was added dropwise. The reaction mixture was stirred under reflux (monitored by TLC). The reaction was quenched with saturated NH_4Cl water solution and extracted with diethylether (10 ml). Combined organic layers were dried over Na_2SO_4 and the solvent was removed by rotary evaporation.

(4,5-*syn*),(5,6-*anti*)-4-Acetyl-5-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (4a). 105 mg (32%), colourless solid, mp 81-83 °C, $[\alpha]_D$ = +260.71 (*c* 0.10); for $C_{19}H_{25}NO_4$ (Mw 331.45) w_i(calc.): 68.86% C, 7.60% H, 4.23% N; w_i(found): 68.45% C, 7.45% H, 4.11% N; IR (ν/cm^{-1}): 2993 (H-C=), 2961, 2936, 2882 (H-C), 1719 (CO), 1611 (C=N); ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.36 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 1.90 (s, 3H, $COCH_3$), 2.29 (s, 3H, 4-$CH_3C_6H_4$), 2.38 (s, 6H, 2,6-di$CH_3C_6H_3$), 3.94 (dd, 1H, H-7b, $J_{6,7b}$ = 4.3 Hz, $J_{7a,7b}$ = 8.8 Hz), 4.18 (dd, 1H, H-7a, $J_{6,7a}$ = 6.3 Hz), 4.23 (ddd, 1H, H-6, $J_{5,6}$ = 7.4 Hz), 4.59 (d, 1H, H-4, J = 7.4 Hz), 5.11 (dd, 1H, H-5), 6.91 (s, 2H, H-Ph.).

(4,5-*syn*),(5,6-*anti*)-4-Furoyl-5-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (4b). 146 mg, (38%), colourless viscous sirup; for $C_{19}H_{25}NO_4$ (Mw 331.45) w_i(calc.): 68.86% C, 7.60% H, 4.23% N; w_i(found): 69.05% C, 7.37% H, 4.59% N; ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.36 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.20 (s, 3H, 4-CH_3-

Ph), 2.21 (s, 6H, 2,6-CH_3-Ph), 3.95 (dd, 1H, H-7b, $J_{6,7b}$ = 4.5 Hz, $J_{7a,7b}$ = 8.8 Hz), 4.19 (dd, 1H, H-7a, $J_{6,7a}$ = 6.3 Hz), 4.35 (ddd, 1H, H-6, $J_{5,6}$ = 6.9 Hz), 5.22 (d, 1H, H-4, $J_{4,5}$ = 10.4 Hz), 5.23 (dd, 1H, H-5), 6.37 (dd, 1H, H-4 furan, $J_{3,4}$ = 3.8 Hz, $J_{4,5}$ = 1.6 Hz), 7.01 (d, 1H, H-3 furan), 7.38 (d, 1H, H-5 furan), 6.76 (s, 2H, H-Ph.).

(4,5-*syn*),(5,6-*syn*)-4-Acetyl-5-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (5a). 22 mg (7%), colourless foam; ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.39 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.85 (s, 3H, $COCH_3$), 2.24 (s, 3H, 4-$CH_3C_6H_4$), 2.29 (s, 6H, 2,6-di$CH_3C_6H_3$), 4.12 (d, 1H, H-7b, $J_{6,7b}$ = 6.7 Hz, $J_{7a,7b}$ = 8.5 Hz), 4.15 (d, 1H, H-7a, $J_{6,7a}$ = 6.7 Hz), 4.29 (ddd, 1H, H-6, $J_{5,6}$ = 2.8 Hz), 4.66 (d, 1H, H-4, J = 8.0 Hz), 5.25 (dd, 1H, H-5), 6.91 (s, 2H, H-Ph.).

(4,5-*syn*),(5,6-*syn*)-4-Furoyl-5-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (5b). 45mg (12%), colourless oil; for $C_{22}H_{25}NO_5$ (Mw 383.44) w_i(calc.): 68.91% C, 6.57% H, 3.65% N; w_i(found): 69.05% C, 6.31% H, 3.59% N; ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.19 (s, 3H, 4-$CH_3C_6H_4$), 2.22 (s, 6H, 2,6-diCH_3 C_6H_3), 4.16 (d, 2H, H-7a, H-7b, $J_{6,7a}$ = $J_{6,7b}$ = 6.9 Hz), 4.37 (ddd, 1H, H-6, $J_{5,6}$ = 2.8 Hz,), 5.30 (d, 1H, H-4, $J_{4,5}$ = 7.7 Hz), 5.37 (dd, 1H, H-5), 6.36 (dd, 1H, H-4 furan, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 1.6 Hz), 6.74 (s, 2H, H-Ph,), 6.99 (d, 1H, H-3 furan), 7.37 (d, 1H, H-5 furan).

(4,5-*syn*),(4,6-*anti*)-5-Acetyl-4-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (6a). 92 mg (28%), viscous sirup; for $C_{19}H_{25}NO_4$ (Mw 331.45) w_i(calc.): 68.86% C, 7.60% H, 4.23% N; w_i(found): 68.65% C, 7.38% H, 4.31% N; ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.11 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.44 (s, 3H, 4-$CH_3C_6H_4$), 2.29 (s, 9H, $COCH_3$, 2,6-di$CH_3C_6H_3$), 3.28 (dd, 1H, H-7b, $J_{6,7b}$ = 8.0 Hz, $J_{7a,7b}$ = 8.0 Hz), 3.81 (dd, 1H, H-7a, $J_{6,7a}$ = 5.8 Hz), 4.15 (dd, 1H, H-4, $J_{4,5}$ = 4.9 Hz, $J_{4,6}$= 5.0 Hz), 4.23 (ddd, 1H, H-6), 4.99 (d, 1H, H-5), 6.87 (s, 2H, H-Ph.).

(4,5-*syn*),(4,6-*anti*)-5-Furoyl-4-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (6b). 95 mg (25%), colourless sirup; for $C_{22}H_{25}NO_5$ (Mw 383.44) w_i(calc.): 68.91% C, 6.57% H, 3.65% N; w_i(found): 69.24% C, 6.37% H, 3.25% N; ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 0.96 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.28 (s, 9H, 2,4,6-tri$CH_3C_6H_2$), 3.41 (dd, 1H, H-7b, $J_{6,7b}$ = 6.6 Hz, $J_{7a,7b}$ = 8.50 Hz), 3.80 (dd, 1H, H-7a, $J_{6,7a}$ = 5.8 Hz), 4.18 (dd, 1H, H-4, $J_{4,5}$= 10.7 Hz, $J_{4,6}$= 7.4 Hz), 4.34 (ddd, 1H, H-6), 5.63 (d, 1H, H-5), 6.63 (dd, 1H, H-4 furan, $J_{3,4}$ = 3.9 Hz, $J_{4,5}$ = 1.7 Hz), 6.85 (s, 2H, H-Ph.), 7.67 (d, 1H, H-3 furan), 7.70 (d, 1H, H-5 furan).

(*R*)-4-Acetyl-5-(6,7-*O*-isopropylidene-6,7-dihydroxyethyl]-3-(2,4,6-trimethylphenyl) isoxazole (12). 44 mg (13%), colourless solid, mp 124-125 °C; for $C_{19}H_{23}NO_4$ (Mw 329.39) w_i(calc.): 69.28% C, 7.04% H, 4.25% N; w_i(found): 68.92% C, 7.25% H, 4.16% N; ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.51 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.83 (s, 3H, $COCH_3$), 2.06, 2.11 (s, 3H, 2,6-di$CH_3C_6H_3$), 2.34 (s, 3H, ,4-$CH_3C_6H_4$), 4.10 (dd, 1H, H-7b, $J_{6,7b}$ = 5.5 Hz, $J_{7a,7b}$ = 8.8 Hz), 4.55 (dd, 1H, H-7a, $J_{6,7a}$ = 6.9 Hz), 5.76(dd, 1H, H-6, $J_{6,7a}$ = 6.9 Hz, $J_{6,7b}$= 5.5 Hz), 6.97, 6.98 (s, 1H, H-Ph); ^{13}C NMR (75 MHz; $CDCl_3$) δ/ppm: 20.2 (2-$CH_3C_6H_4$), 20.3 (6-$CH_3C_6H_4$), 21.5 (4-$CH_3C_6H_4$), 25.7, 26.5 (CH_3), 29.1 ($COCH_3$), 69.2 (C-7), 71.7 (C-6), 111.9 [C(CH3)2],

117.9 (C-4), 125.5 (C-4-Ph), 128.9 (C-3-Ph), 129.0 (C-5-Ph), 137.1 (C-2-Ph), 137.4 (C-6-Ph), 140.1 (C-1-Ph), 161.0 (C-3), 176.3 (C-5), 193.2 (CO).

(4,5-*syn*),(4,6-*syn*)-5-Furoyl-4-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (7b). 192 mg (50%), colourless viscous sirup; for colourless sirup; for $C_{22}H_{25}NO_5$ (Mw 383.44) w_i(calc.): 68.91% C, 6.57% H, 3.65% N; w_i(found): 68.74% C, 6.74% H, 3.44%; ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.14 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 2.23 (s, 3H, 4-$CH_3C_6H_4$), 2.35 (s, 6H, 2,6-di$CH_3C_6H_3$), 4.09 (dd, 1H, H-7b, $J_{6,7b}$ = 4.1 Hz, $J_{7a,7b}$ = 9.1 Hz), 4.15 (dd, 1H, H-7a, $J_{6,7a}$ = 3.6 Hz), 4.38 (m, 1H, H-6), 4.95 (dd, 1H, H-4, $J_{4,5}$ = 10.9 Hz, $J_{4,6}$ = 9.3 Hz), 5.62 (d, 1H, H-5), 6.51(dd, 1H, H-4 furan, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 1.7 Hz), 6.83 (s, 2H, H-Ph,), 7.12 (d, 1H, H-3 furan), 7.53 (d, 1H, H-5 furan).

(4,5-*anti*),(5,6-*anti*)-4-Acetyl-5-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (8a). 120 mg (36%), colourless solid, mp 95-97 °C, $[\alpha]_D$ = +326.55 (*c* 0.12); for $C_{19}H_{25}NO_4$ (Mw 331.45) w_i(calc.): 68.86% C, 7.60% H, 4.23% N; w_i(found): 68.99% C, 7.33% H, 4.44% N; IR (ν/cm^{-1}): 2993 (H-C=), 2961, 2938, 2882 (H-C), 1719 (CO), 1610 (C=N); ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.36 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.90 (s, 3H, $COCH_3$), 2.24 (s, 6H, 2,6-di$CH_3C_6H_3$), 2.30 (s, 3H, 4-$CH_3C_6H_4$), 3.94 (dd, 1H, H-7b, $J_{6,7b}$ = 4.1 Hz, $J_{7a,7b}$ = 8.8 Hz), 4.18 (ddd, 1H, H-7a, $J_{6,7a}$ = 4.1 Hz, $J_{5,7a}$= 1.00 Hz), 4.23 (ddd, 1H, H-6, $J_{5,6}$ = 6.6 Hz), 4.59 (d, 1H, H-4, J = 7.1 Hz), 5.11 (dd,1H, H-5), 6.90 (s, 2H, H-Ph.); ^{13}C NMR (75 MHz; $CDCl_3$) δ/ppm: 20.2 (2,6-di$CH_3C_6H_3$), 21.3 (4-$CH_3C_6H_4$), 25.3, 26.9 (CH_3), 30.40 ($COCH_3$), 66.6 (C-4), 67.5 (C-7), 75.6 (C-6), 80.4 (C-5), 110.2 [C(CH3)2], 124.9 (C-4-Ph), 129.2 (C-3, C-5-Ph), 137.2 (C-2, C-6-Ph), 139.7 (C-1-Ph), 153.6 (C-3), 201.0 (CO).

(4,5-*anti*),(5,6-*anti*)-4-Furoyl-5-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (8b). 148 mg (38%), colourless viscous foam, $[\alpha]_D$ = +188.69 (*c* 0.11); for $C_{22}H_{25}NO_5$ (Mw 383.44) w_i(calc.): 68.91% C, 6.57% H, 3.65% N; w_i(found): 68.71% C, 6.42% H, 3.51% N; IR (ν/cm^{-1}): 3021 (H-C=), 2992, 2930, 2882 (H-C), 1678 (CO), 1609 (C=N); ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.36 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 2.20 (s, 3H, 4-$CH_3C_6H_4$), 2.22 (s, 6H, 2,6-diCH_3 C_6H_3), 3.95 (dd, 1H, H-7b, $J_{6,7b}$ = 4.5 Hz, $J_{7a,7b}$ = 8.9 Hz), 4.19 (dd, 1H, H-7a, $J_{6,7a}$ = 6.4 Hz), 4.34 (ddd, 1H, H-6, $J_{5,6}$ = 1.5 Hz), 5.23 (dd, 1H, H-5), 5.26 (d,1H, H-4, $J_{4,5}$ = 5.2 Hz), 6.37 (dd, 1H, H-4 furan, $J_{3,4}$ = 3.6 Hz, $J_{4,5}$ = 1.7 Hz), 6.77 (s, 2H, H-Ph.), 7.06 (d, 1H, H-3 furan), 7.38 (d, 1H, H-5 furan).

(4,5-*anti*),(5,6-*syn*)-4-Acetyl-5-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (9a). 24 mg (7%), colourless solid, mp 83-85 °C; for $C_{19}H_{25}NO_4$ (Mw 331.45) w_i(calc.): 68.86% C, 7.60% H, 4.23% N; w_i(found): 68.41% C, 7.45% H, 4.14% N; IR (ν/cm^{-1}): 2995 (H-C=), 2958, 2932, 2880 (H-C), 1722 (CO), 1618 (C=N) cm^{-1}; ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.39 (s, 3H, CH_3), 1.44 (s, 3H, CH_3), 1.85 (s, 3H, $COCH_3$), 2.24 (s, 6H, 2,6-di$CH_3C_6H_3$), 2.30 (s, 3H, 4-$CH_3C_6H_4$), 4.12 (d, 1H, H-7b, $J_{6,7b}$ = 6.6 Hz, $J_{7a,7b}$ = 8.5 Hz), 4.15 (dd, 1H, H-7a, $J_{6,7a}$ = 6.6 Hz, $J_{5,7a}$= 1.0 Hz), 4.28 (ddd, 1H, H-6, $J_{5,6}$ = 2.8 Hz), 4.65 (d, 1H, H-4, J = 8.0 Hz), 5.25 (dd, 1H, H-5), 6.92 (s, 2H, H-Ph.).

(4,5-*anti*),(5,6-*syn*)-4-Furoyl-5-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (9b). 33 mg, (8%), colourless foam, $[\alpha]_D$ = –287.64 (*c* 0.12); IR

(ν/cm^{-1}): 3023 (H-C=), 2993, 2928, 2882 (H-C), 1678 (CO), 1609 (C=N); ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.40 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 2.19 (s, 3H, 4-CH_3-Ph), 2.22 (s, 6H, 2,6-CH_3-Ph), 4.16 (d, 2H, H-7a, H-7b, $J_{6,7a} = J_{6,7b} = 6.9$ Hz), 4.37 (ddd, 1H, $J_{6,7a} = 6.4$ Hz), 4.34 (ddd, 1H, H-6, $J_{5,6} = 1.5$ Hz), 5.23 (dd, 1H, H-5), 5.26 (d,1H, H-6, $J_{5,6} = 2.8$ Hz), 5.30 (d, 1H, H-4, $J_{4,5} = 7.7$ Hz), 5.37 (dd, 1H, H-5), 6.36 (dd, 1H, H-4 furan, $J_{3,4} = 3.7$ Hz, $J_{4,5} = 1.8$ Hz), 6.74 (s, 2H, H-Ph.), 6.98 (d, 1H, H-3 furan), 7.37 (d, 1H, H-5 furan).

(4,5-*anti*),(4,6-*anti*)-5-Acetyl-4-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (10a). 80 mg (24%), colourless solid, mp 152-154 °C, $[\alpha]_D$ = +117.19 (*c* 0.13); for $C_{19}H_{25}NO_4$ (Mw 331.45) w_i(calc.): 68.86% C, 7.60% H, 4.23% N; w_i(found): 69.05% C, 7.37% H, 4.59% N; IR (νcm^{-1}): 2993 (H-C=), 2961, 2940, 2884 (H-C), 1720 (CO), 169 (CN); ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.28 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.22 (s, 3H, $COCH_3$), 2.29 (s, 6H, 2,6-di$CH_3C_6H_3$), 2.44 (s, 3H, 4-$CH_3C_6H_4$), 3.50 (dd, 1H, H-7b, $J_{6,7b} = 6.3$ Hz, $J_{7a,7b} = 8.5$ Hz), 3.84 (dd, 1H, H-4, $J_{4,5} = 4.9$ Hz, $J_{4,6} = 4.1$Hz), 3.87 (dd, 1H, H-7a, $J_{6,7a} = 6.3$ Hz), 4.13 (ddd, 1H, H-6), 5.03 (d,1H, H-5), 6.90 (s, 2H, H-Ph.); ^{13}C NMR (75 MHz; $CDCl_3$) δ/ppm: 20.2 (2,6-$CH_3C_6H_3$), 21.4 (4-$CH_3C_6H_4$), 25.2, 26.7 (CH_3), 27.1 ($COCH_3$), 57.2 (C-4), 67.5 (C-7), 73.0 (C-6), 85.2 (C-5), 110.0 [C(CH3)2], 124.3 (C-4-Ph), 129.1 (C-3, C-5-Ph), 139.4 (C-1-Ph), 157.5 (C-3), 208.7 (CO).

(4,5-*anti*),(4,6-*anti*)-5-Furoyl-4-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (10b). 70 mg (18%), colourless foam, $[\alpha]_D$ = +313.11 (*c* 0.11); for $C_{22}H_{25}NO_5$ (Mw 383.44) w_i(calc.): 68.91% C, 6.57% H, 3.65% N; w_i(found): 68.78% C, 6.34% H, 3.55% N; IR (ν/cm^{-1}): 3021 (H-C=), 2992, 2930 (H-C), 1676 (CO), 1611 (C=N); ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.29 (s, 3H, CH_3), 1.45 (s, 3H, CH_3), 2.26 (s, 6H, 2,6-diCH_3 C_6H_3), 2.29 (s, 3H, 4-$CH_3C_6H_4$), 3,47 (dd, 1H, H-7b, $J_{6,7b} = 6.0$ Hz, $J_{7a,b} = 8.8$ Hz), 3.87 (dd, 1H, H-7a, $J_{6,7a} = 6.6$ Hz), 4.20 (dd, 1H, H-4, $J_{4,5} = 5.5$ Hz, $J_{4,6} = 4.4$ Hz), 4.26 (ddd, 1H, H-6), 5.64 (d, 1H, H-5), 6.63 (dd, 1H, H-4 furan, $J_{3,4} = 3.8$ Hz, $J_{4,5} = 1.6$ Hz), 6.90 (s, 2H, H-Ph.), 7.67 (d, 1H, H-3 furan), 7.72 (d, 1H, H-5 furan).

(4,5-*anti*),(4,6-*syn*)-5-Acetyl-4-(6,7-*O*-isopropylidene-6,7-dihydroxyetyl)-3-(2,4,6-trimethylphenyl)isoxazoline (11a). 7 mg (2%), colourless oil; ^{1}H NMR (300 MHz; $CDCl_3$) δ/ppm: 1.29 (s, 3H, CH_3), 1.41 (s, 3H, CH_3), 1.78 (s, 3H, $COCH_3$), 2.27 (s, 3H, 4-$CH_3C_6H_4$,), 2.41 (s, 6H, 2,6-di$CH_3C_6H_3$), 3.37 (dd, 1H, H-7b, $J_{6,7b} = 7.1$ Hz, $J_{7a,7b} = 8.8$ Hz), 3.64 (dd, 1H, H-4, $J_{4,5} = 5.5$ Hz, $J_{4,6} = 6.30$ Hz), 3.70 (dd, 1H, H-7a, $J_{6,7a} = 6.3$ Hz), 4.15 (ddd, 1H, H-6), 4.94 (d, 1H, H-5), 6.90 (s, 2H, H-Ph.); ^{13}C NMR (75 MHz; $CDCl_3$) δ/ppm: 20.4 (2,6-diCH_3 C_6H_3), 21.3 (4-$CH_3C_6H_4$), 25.4, 26.6 (CH_3), 27.1 ($COCH_3$), 56.9 (C-4), 67.6 (C-7), 74.0 (C-6), 83.9 (C-5), 109.6 [C(CH3)2], 124.6 (C-4-Ph), 128.9 (C-3, C-5-Ph), 139.0 (C-2, C-6-Ph), 140.9 (C-1, Ph), 156.2 (C-3).

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