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# Reaction of *N*-heterocyclic carbaldehydes with furanones – an investigation of reactivity and regioselectivity

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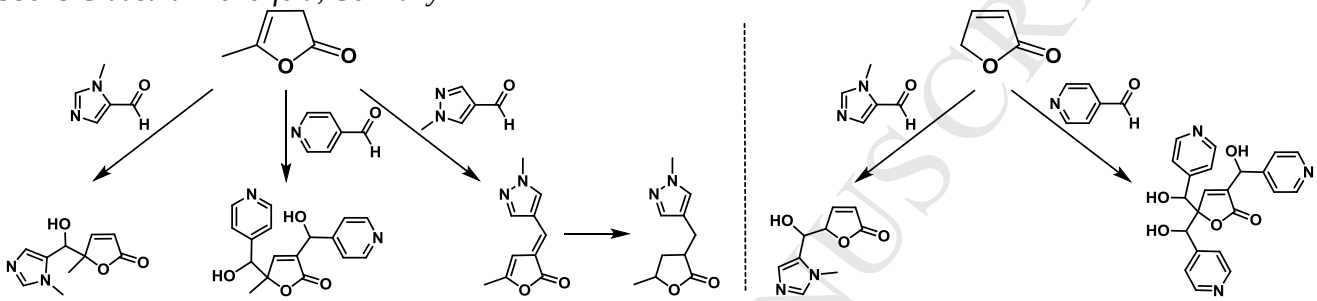

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# Reaction of *N*-heterocyclic carbaldehydes with furanones – an investigation of reactivity and regioselectivity

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ABSTRACT

The aldol reaction of *N*-heterocyclic carbaldehydes with furan-2-ones has been investigated. Very mild and metal-free reaction conditions have been applied. The substitution pattern of the product was found to be controlled by the aldehyde. A detailed investigation of the reactivity has been performed and the surprising regio- and diastereoselectivity has been elucidated with the help of 2D-NMR techniques. Here, we report on a convenient way to *N*-donor functionalized lactones, which had scarcely been examined before.



## 1. Introduction

The base catalyzed aldol reaction of various aldehydes with 5-membered ring lactones such as γ-butyrolactone (**1**), α-angelica lactone (**2**), and γ-crotonolactone (**3**) is a long known and convenient way to α- and γ-substituted butyrolactones. The resulting structure motif is found in several bioactive compounds such as losigamone as potential anticonvulsant,[1] metabolites of epicatechin[2] and precursors for drugs such as physovenine analogs[3], protease inhibitors[4] and several more[5–7] (Figure 1).

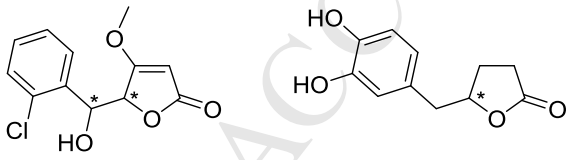



**Fig 1.** Losigamone (left) and one metabolite of epicatechin (right).

The reaction of γ-butyrolactone (**1**) with aliphatic and nitrogen-free aromatic aldehydes has been investigated in detail. Upon deprotonation in α-position (typically with sodium methoxide), the aldol condensation products α-arylidene/α-alkylidene-dihydrofurans are formed in good yields.[3,8] At low temperatures, the product of the aldol addition may be isolated. The choice of the present metal ions ($Li^+$ vs. additional $Zn^{2+}$) allows controlling *syn*/*anti* configuration of the resulting α-(aryl-hydroxymethyl)dihydrofuranones.[9] Various aldehydes and variants of the reaction conditions, in some cases by activation of γ-butyrolactone *via* reactive intermediates, have been applied.[10–14]

The aldol reaction of α-angelica lactone (**2**) with aliphatic and nitrogen-free aromatic aldehydes can be performed at milder conditions. In the presence of sodium acetate, several α-arylidene-5-methylfuran-2(3*H*)-ones have been isolated.[15] In the presence of amines such as $HNEt_2$ or $NEt_3$ as base, condensation towards the α-substituted derivates has been achieved.[16–20] In the additional presence of $Bu_2BOTf$ and at low temperatures, aldol addition with aliphatic aldehydes towards the α-(1-hydroxyalkyl)-5-methylfuran-2(3*H*)-ones takes place.[21] By reaction with enals such as 1-pentenal and in presence of an organocatalyst, vinylogous Michael aldol addition in γ-position has been observed.[22] In the case of γ-crotonolactone (**3**), the lithiated butenolide has been reported to react with aliphatic aldehydes towards a mixture of α-(1-hydroxyalkyl)furan-2(5*H*)-ones and γ-(1-hydroxyalkyl)furan-2(5*H*)-ones at low temperatures.[23,24] Aromatic aldehydes preferably form the γ-adduct at the same reaction conditions.[2,24] Applying milder conditions at ambient temperature with secondary or tertiary amines as base, aromatic non-*N*-heterocyclic aldehydes lead to the γ-adduct, again. Condensation towards the γ-arylidene-furan-2(5*H*)-ones is likely to happen subsequently.[25–28] α,β-Unsaturated aldehydes lead to γ-Michael addition under comparable conditions.[29] In the presence of boron and tin compounds, mixtures of α- and γ-addition with a preference for the α-position have been obtained.[30] Various (organo)catalysts featuring γ-addition of nitrogen-free aromatic aldehydes providing additional diastereo- and/or enantioselectivity of the resulting γ-(1-aryl-1-hydroxymethyl)butenolides are known.[31–35] Furthermore, α-addition may be forced by a synthetic pathway *via* aluminum

enolates.[36,37] Frequently, the butenolide is converted into a 2-trialkylsilyloxyfuran prior to aldol addition.[38–40] In the presence of dialkylzinc, aldol addition in α-position takes place, accompanied by reduction of the double bond.[41,42] In a three-component reaction, PhSLi and aryl aldehydes lead to α-addition of the aldehyde, accompanied by β-addition of the thiolate.[43] Due to the large interest in the structure motif, additional pathways to a large variety of α-arylidenefuran-2(3*H*)-ones have been investigated.[44]

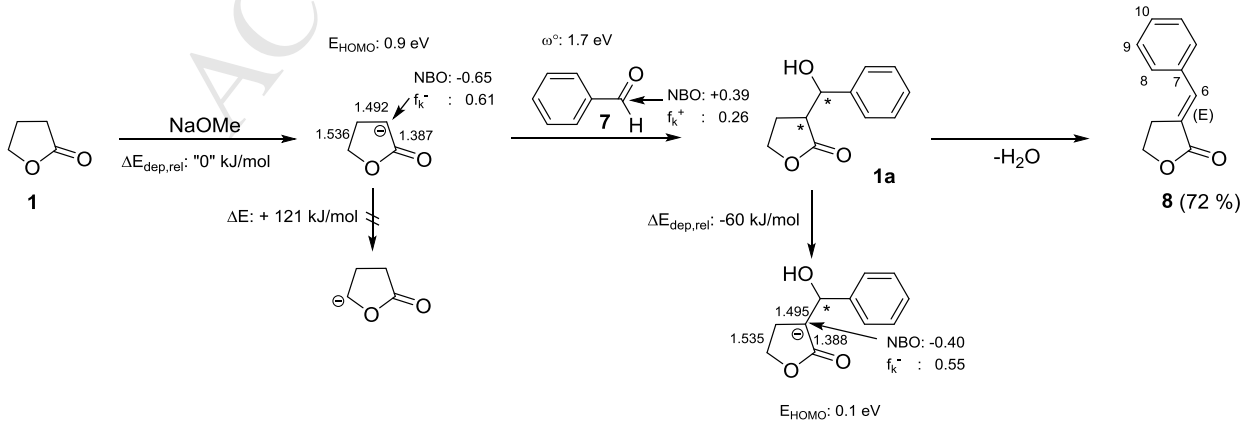
Surprisingly, the reaction of *N*-heterocyclic aldehydes with the aforementioned lactones has scarcely been investigated up to now. Pyridinecarboxaldehydes have been reported to yield unidentified tars upon reaction with γ-butyrolactone (**1**) in the presence of NaOMe.[8] One reference claims the reaction of pyridinecarboxaldehydes with α-angelica lactone (**2**) in the presence of $HNEt_2$ towards the α,α-bis-substituted lactones, probably by two consecutive aldol additions, to take place.[45] Benzofuran-2(3*H*)-one yields the α-pyridinylmethylene substituted derivatives upon treatment with pyridinecarboxaldehydes[46] *via* aldol condensation in analogy to the synthesis of marginalin from 2-coumaranone and *p*-hydroxybenzaldehyde.[47] γ-Crotonolactone (**3**) reacts in a two-step conjugated addition-alkylation with lithiated dithianes and pyridinecarboxaldehydes to the α-(1- hydroxy-1-pyridinylmethyl)-β-(dithianyl)dihydrofuranones.[48,49]

Here, we present an investigation of the reactivity and surprising regioselectivity of the reaction of 4-pyridinecarboxaldehyde (**4**), *N*-methylpyrazole-4-carboxaldehyde (**5**), and *N*-methylimidazole-5-carboxaldehyde (**6**) with α-angelica lactone (**2**) and γ-crotonolactone (**3**) under very mild and metal-free conditions. Our motivation is based on the prospective use of the *N*-donor functionalized lactones as comonomers for the ring-opening polymerization[50,51] with lactide to yield metal ion crosslinked and stabilized polylactides. These are of certain interest as improved 3D-printing materials.[52–54]

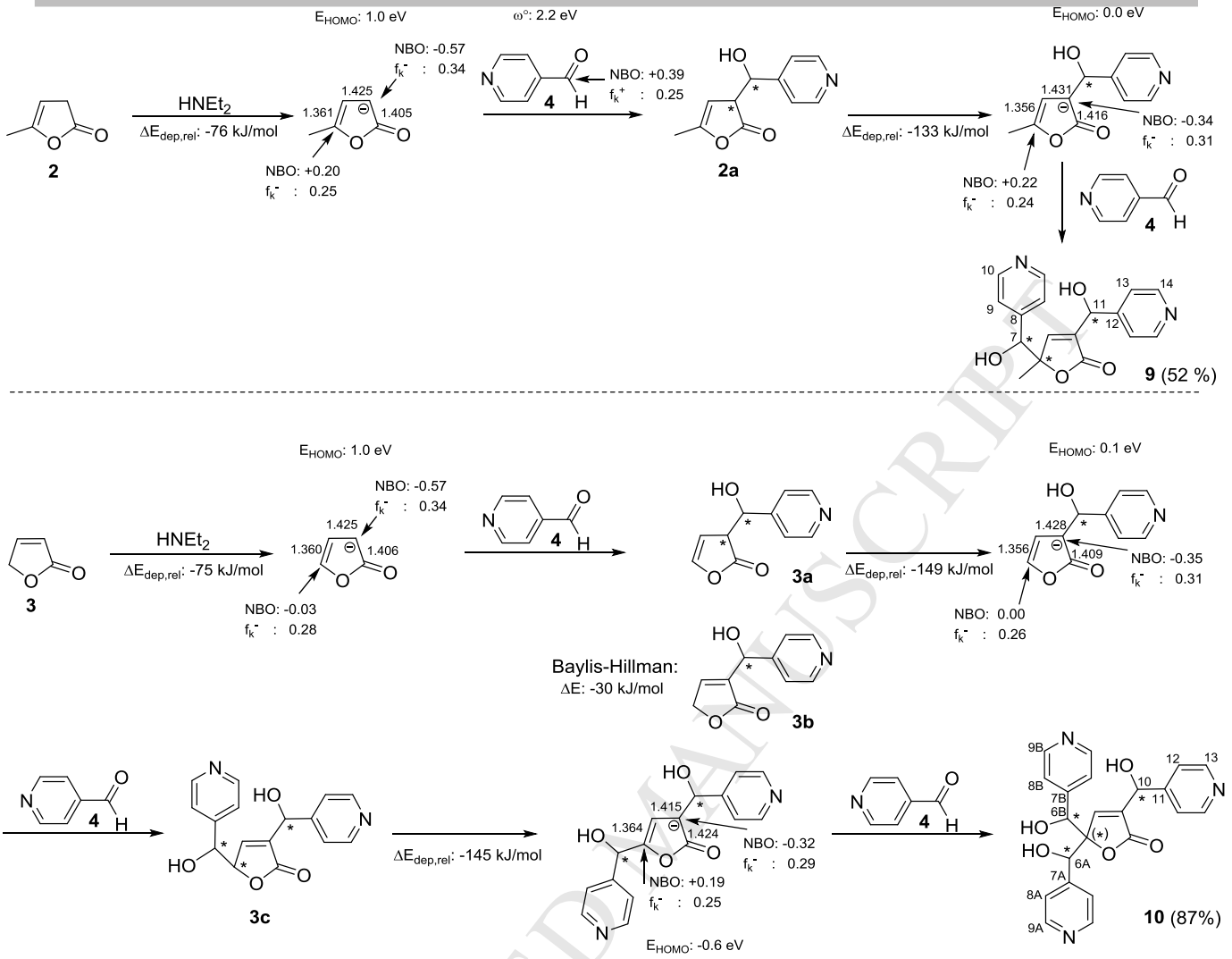
## 2. Results and Discussion

The well-known reaction of γ-butyrolactone (**1**) with benzaldehyde (**7**) was chosen as starting point (Scheme 1). According to literature, (*E*)-3-benzylidendihydrofuran-2-one (**8**) is formed in good yields in the presence of NaOMe as base. Basically, we followed a known literature procedure,[14] but performed the reaction at 0 °C to maintain exactly the same temperature profile for all reactions discussed. The sole isolated condensation product **8** was confirmed to have *E*-configuration by a strong NOE visible in $^1$H,$^1$H-Nuclear Overhauser Effect Spectroscopy (NOESY) between the *o*-benzyl protons and the protons in β-position of the lactone ring. To compare the stability of the anions, the deprotonation energies ($\Delta E_{dep,rel}$) were calculated on the LACVP**/PBE0 level of theory and are discussed relative to the deprotonation energy of **1** in α-position. The reactivity of the aldehydes towards an attack of a nucleophile was estimated by the global electrophilicity index ω°,[55] and the reactivity of the nucleophilic anions by the energy of the highest occupied molecular orbital (HOMO).[56] To compare the nucleophilicity of the α- and γ-position, additionally Fukui indices[57] ($f_k^-$) and plots of the Fukui $f^-$ function[58] have been calculated if appropriate. The anion of **1** shows an obvious indication for enolization, visible by the calculated **C**O-**C**$_\alpha$ bond length of 1.387 Å. Nevertheless, $C_\alpha$ is still in posession of a negative charge of -0.65 e (NBO charges) and is the most nucleophilic position ($f_k^- = 0.61$). Interestingly, after formation of α-(hydroxy(phenyl)methyl)dihydrofuranone (**1a**) as isolable intermediate[9] the deprotonation of the remaining hydrogen in α-position is favoured by 60 kJ/mol compared to **1**. In practice, no indication for twofold addition is found. This is explained by the strongly reduced nucleophilicity of the anion of **1a**, indicated by a lowering of the energy of the HOMO by 0.8 eV. Accordingly, condensation towards the conjugated benzylidene **8** is favoured instead of a second nucleophilic attack of **7**. Performing the same reaction with 4-pyridinecarboxaldehyde (**4**) instead of benzaldehyde (**7**) did not lead to any well-defined reaction products, even at low temperatures. This is in consistency with literature.[8] Chosing mild reaction conditions with diethylamine as weak base did not lead to any reaction with **4** or **7** at all.

Consequently, α-angelica lactone (**2**) was chosen as substrate. Delocalization stabilizes the anion of **2** by 76 kJ/mol (Scheme 2). According to literature, the formation of the α,α-bis(pyridinyl)-substituted lactone should be expected upon treatment of **2** with **4** in presence of $HNEt_2$.[45] While the isolated product revealed a mass peak of m/z = 313.0 matching the proposed structure, NMR spectra revealed a mixture of isomers in the ratio of roughly 1:1. With the help of reversed phase column chromatography, one isomer could be purified and finally the structure was resolved as the α,γ-bis-substituted derivative 3,5-bis(hydroxy(pyridin-4-yl)methyl)-5-methylfuran-2(5*H*)-one (**9**). According to the NMR data, both obtained diastereomers belong to the same type of regioisomer. In both cases a clear set of cross signals of $\mathbf{H}_{Me}$ with 7-**C** and 7-**H** with $\mathbf{C}_{Me}$ is observed in the Heteronuclear Multi Bond Correlation ($^1$H,$^{13}$C-HMBC) NMR spectra. The formation of this regioisomer may be described by a pathway given in Scheme 2. The anion of **2** shows a rather strong localization of the negative charge in α-position (-0.57 e).




**Scheme 1.** Reaction of benzaldehyde (**7**) with γ-butyrolactone (**1**).




**Scheme 2.** Reaction of 4-pyridinecarboxaldehyde (**4**) with α-angelica lactone (**2**) (top) and γ-crotonolactone (**3**) (bottom).

Nevertheless, the nucleophilicity of the α- and γ-position is quite similar according to their Fukui indices and even more with regard to the more accurate Fukui f⁻ function (Figure 2). The reactivity of the anion is quite comparable to the reactivity of the anion of γ-butyrolactone (**1**) according to the energy of the HOMO. Upon reaction at the α-position (which may be assumed, since addition in γ-position would lead to an olefinic hydrogen in α-position which is unlikely to be deprotonated subsequently), 3-(hydroxy(pyridin-4-yl)methyl)-5-methylfuran-2(3*H*)-one (**2a**) is formed. The deprotonation of this intermediate is again favoured by ~60 kJ/mol compared to **2** whereas the reactivity of the anion is reduced. This is indicated by the lowering of the energy of the HOMO of the anion of **2a** by 1.0 eV. Nevertheless, a second aldol addition can take place because the reactivity of 4-pyridinecarboxaldehyde (ω° = 2.2 eV) is significantly increased compared to benzaldehyde (ω° = 1.7 eV) according to their global electrophilicity indices. This is in consistency with an electron-poor 6-membered ring *N*-heterocyclic aromatic carbaldehyde. The increased reactivity overcompensates the decrease of nucleophilicity of the anion of **2a**. Again, the second nucleophilic attack may be induced from α- or γ-position according to the Fukui f⁻ function (Figure 2). Reaction at γ-position finally leads to regioisomer **9** as a mixture of two diastereomers. Switching to γ-crotonolactone (**3**) as substrate for the reaction with 4-pyridinecarboxaldehyde (**4**) leads to a comparable reactivity (Scheme 2). The main mass peak at m/z = 406.2 indicated threefold aldol addition. The sole isolated reaction product was identified as one main diastereomer of 3,5,5-tris(hydroxy(pyridin-4-yl)methyl)furan-2(5*H*)-one (**10**). Due to three rather similar pyridine moieties, the NMR data were not straightforward to assign. The two hydroxymethylpyridine residues in γ-position are either heterotopic (*R**/*S**) attached to $C_\gamma$ as stereo centre or diastereotopic (*R**/*R**) with $C_\gamma$ as non-stereogenic in this case, but leading to a unique set of signals in the NMR spectra in any case. Identification of the spin systems *via* Total Correlation Spectroscopy (TOCSY) and $^{1}H,^{15}N$-HMBC allowed to determine the regioisomer **10** unambiguously. Significant proofs are two cross signals of **H**OC$_{6A}$ and **H**OC$_{6B}$ with **C**$_\gamma$ and just one cross signal of 10-**H** with **C**=O in the $^{1}H,^{13}C$-HMBC NMR spectra as well as the allylic $^{4}J_{H,H}$ coupling of 10-**H** with **H**$_\beta$. The reaction sequence may be discussed in analogy to the reactivity of α-angelica lactone (**2**) (Scheme 2). The Fukui f⁻ function of the anion of **3** is closely related to the electron density of the HOMO (see Fig. S2 and S3 of the supplementary material) and features nucleophilicity in α- and γ-position. It should be noted, that for the reaction of the first equivalent of **3** with **4** an alternative pathway according to Baylis-Hillman leading to 3-(hydroxy(pyridin-4-yl)methyl)furan-2(5*H*)-one (**3b**) may be followed. The reaction conditions applied here are rather close to typical Baylis-Hillman conditions with

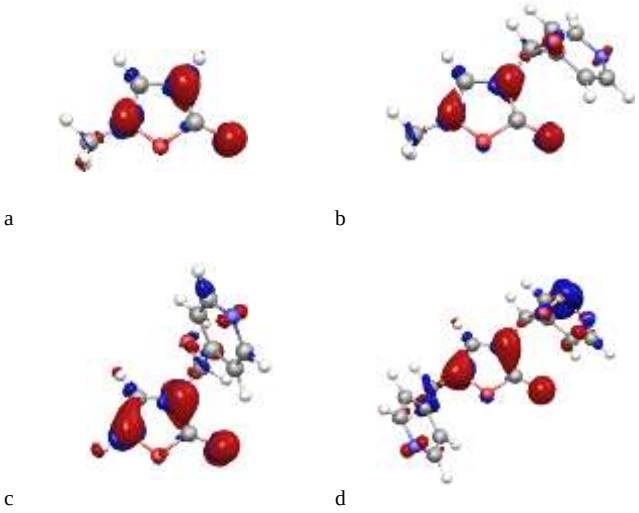
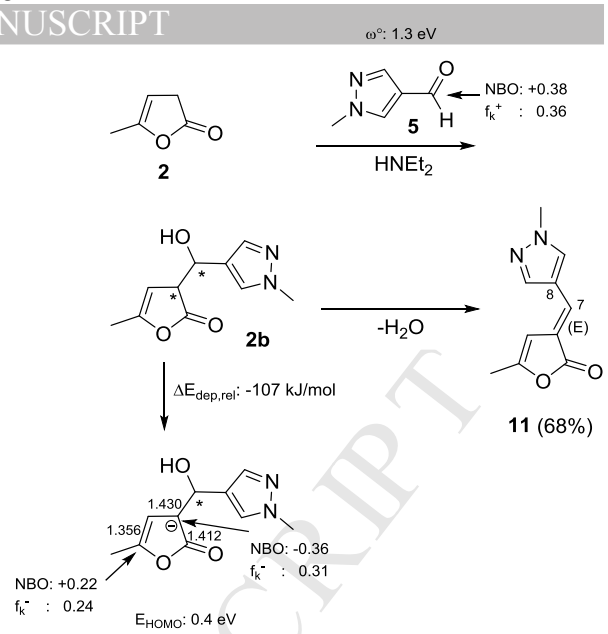



**Fig 2.** Plot of the Fukui f⁻ function of the anion of α-angelica lactone (**2**) (a), 3-(hydroxy(pyridin-4-yl)methyl)-5-methylfuran-2(3*H*)-one (**2a**) (b), 3-(hydroxy(pyridin-4-yl)methyl)furan-2-one (**3a**/**b**) (c), and 3,5-bis(hydroxy(pyridin-4-yl)methyl)furan-2(5*H*)-one (**3c**) (d). Areas in red indicate large negative values and correspond to nucleophilic centres.

sterically demanding amines as base. Furan-2(5*H*)-one (**3**) has been applied as substrate for Baylis-Hillman reactions with benzaldehyde (**7**) in presence of more complex catalytic systems.[59,60] The Baylis-Hillman product **3b** is more stable by 30 kJ/mol compared to the product of the aldol addition in α-position (**3a**) due to conjugation, but in either case deprotonation of both 3-(hydroxy(pyridin-4-yl)methyl)furan-2-ones (**3a**/**3b**) is favoured in comparison to **3** and the same anion is achieved. The Fukui f⁻ function indicates a comparable nucleophilicity of the α- and γ-position again (Figure 2). Since aldol addition in α-position would not allow for a subsequent third aldol addition, and in analogy to the reaction of **2**, 3,5-bis(hydroxy(pyridin-4-yl)methyl)furan-2(5*H*)-one (**3c**) may be assumed to be formed as intermediate. The reactivity of the corresponding anion is reduced with each substitution step. For the anion of **3c**, the energy of the HOMO is lowered by 1.6 eV compared to the anion of **3**. Even this strong reduction of the nucleophilicity is overcompensated by the highly reactive 4-pyridinecarboxaldehyde. The third nucleophilic attack may be induced from α- or γ-position according to the Fukui f⁻ function (Figure 2) and finally **10** is formed by aldol addition in γ-position.

Special attention is given to the striking fact, that only one diastereomer of **10** is isolated in 87 % yield. Starting from the beginning of the reaction sequence for the formation of **3a**, some *syn*/*anti* preference comparable to classic or Mukaiyama aldol addition of cyclic enolates may be discussed (despite the absence of chelating metal ions). In any case, the deprotonation of **3a** leads to an intermediate anion with just one remaining stereo centre adjacent to the α-position. To explain the overall diastereoselectivity, an 1,5-induction for the subsequent second aldol addition may be assumed. Consequently, the stereochemistry of the second stereo centre attached to the γ-position (**3c**) would be controlled by the α-substituent. It is noteworthy to point out the structural similarity of the system with the well-known 1,5-asymmetric induction of aldol reactions with boron enolates reported by Evans and Paterson.[61,62] The third aldol addition may be controlled by an 1,3-induction of the




**Scheme 3.** Reaction of *N*-methylpyrazole-4-carboxaldehyde (**5**) with α-angelica lactone (**2**).

first hydroxymethylpyridine moiety in γ-position. For the two hydroxymethylpyridine residues in γ-position of **10**, finally (*R**/*R**) configuration has to be assumed to reduce the number of possible diastereomers. From the NMR data, it is not possible to determine wether the overall configuration of the hydroxymethylpyridine units is ($R_\alpha$*/$R_\gamma$*/$R_\gamma$*) or ($S_\alpha$*/$R_\gamma$*/$R_\gamma$*). The discussion of the stereochemical induction nicely matches with the observation of two diastereomers for **9**. Again, the hydroxymethylpyridine moiety in α-position of the anion of **2a** may control the configuration of the second hydroxymethylpyridine unit introduced in γ-position by 1,5-induction. Since $C_\gamma$ itself remains as a stereo centre in this case, the number of possible stereoisomers is not reduced and the two adjacent stereocentres lead to the two isolated diastereomers. The overall configuration of **9** consequently is ($R_\alpha$*/$R_{C,\gamma}$*/$R_\gamma$*) or ($S_\alpha$*/$R_{C,\gamma}$*/$R_\gamma$*) for one diastereomer and ($R_\alpha$*/$S_{C,\gamma}$*/$R_\gamma$*) or ($S_\alpha$*/$S_{C,\gamma}$*/$R_\gamma$*) for the second diastereomer.

It should be noted, that a second explanation for the isolation of just one diastereomer of **10** and two diastereomers of **9** may be given by the assumption of apparent-equivalent diastereoisomers.[63] In these cases, isolated stereocentres of a set of diastereomers lead to identical NMR spectra. Consequently, it would not be possible to distinguish between ($R_\alpha$*/$R_\gamma$*/$R_\gamma$*) and ($S_\alpha$*/$R_\gamma$*/$R_\gamma$*) configuration of **10.** Since the minimum distance of at least five carbon atoms between the stereogenic atoms has been determined to achieve segregation of the stereoclusters,[63] this seems rather unlikely in the case of **9** and **10** (bridge of three carbon atoms).

The reactivity of *N*-methylpyrazole-4-carboxaldehyde (**5**) as electron-rich 5-membered ring *N*-heterocyclic aromatic carbaldehyde significantly differs from 4-pyridinecarboxaldehyde (**4**). For the reaction of **5** with α-angelica lactone (**2**), the Knoevenagel condensation product (*E*)-5-methyl-3-((*N*-methylpyrazol-4-yl)methylene)furan-2(3*H*)-one (**11**) is obtained in acceptable yields (Scheme 3). The reactivity is explained rather straightforward keeping in mind the electronic properties given in Scheme 2 as discussed before. After deprotonation of **2**, nucleophilic attack of **5** is induced from α-position. The deprotonation of the intermediate 5-methyl-3-(hydroxy(*N*-methylpyrazol-4-yl)methyl)furan-2(3*H*)-one (**2b**) is favoured again, but the reduced nucleophilicity of the anion of **2b**

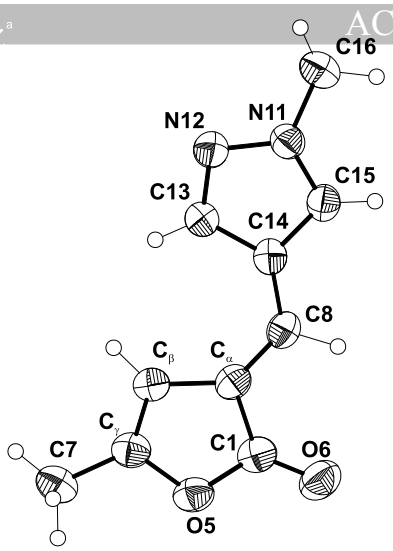
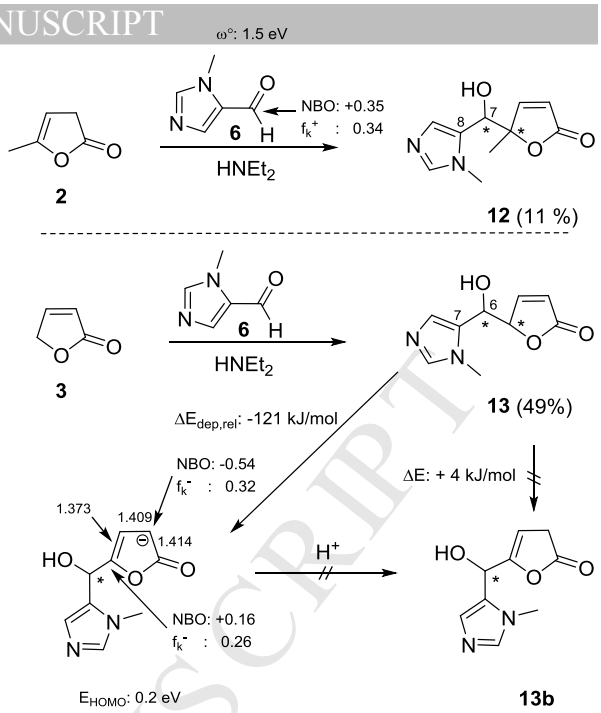



**Fig. 3.** Molecular structure of (*E*)-5-methyl-3-((*N*-methylpyrazol-4-yl)methylene)furan-2(3*H*)-one (**11**); thermal ellipsoids are drawn at the 50 % probability level. Selected bond lengths [Å], angles [°] and dihedral angles [°]: d(C1–$C_\alpha$) = 1.478(6), d($C_\alpha$–$C_\beta$) = 1.451(12), d($C_\beta$–$C_\gamma$) = 1.332(0), d($C_\alpha$–C8) = 1.350(2), d(C1–O6) = 1.220(12), ∠($C_\beta$,$C_\alpha$,$C_\gamma$) = 133.90(1), ∠($C_\alpha$,C8,C14) = 128.80(2), θ($C_\beta$,$C_\alpha$,C14,C13) = 0.01(1), θ(O6,C1,$C_\alpha$,C8) = -0.97(3), θ($C_\beta$,$C_\alpha$,C8,C14) = 0.52(3).

($E_{HOMO}$ is lowered by 0.6 eV compared to the anion of **2**) prohibits a second nucleophilic attack of **5**. The reactivity of **5** (ω° = 1.3 eV) is remarkably lower than of 4-pyridinecarboxaldehyde (**4**). Consequently, the elimination of water probably according to an E1cb-mechanism from the stabilized anion of **2b** towards the highly conjugated condensation product **11** is favoured. A strong NOE of the pyrazole protons with the β-H of the lactone ring has been observed by NOESY, and consequently *E*-configuration has been assumed. Finally, a single-crystal X-ray structure determination unambiguously revealed the regio- and stereochemistry of **11** (Figure 3). The dihedral angle $C_\beta$-$C_\alpha$-C14-C13 = 0.01(1) ° demonstrates the perfect planarity of the molecule due to the delocalized π-electron system throughout the whole molecular structure.

For the reaction of *N*-methylimidazole-5-carboxaldehyde (**6**) with α-angelica lactone (**2**) again a single aldol reaction step is expected due to the low reactivity of **6** (ω° = 1.5 eV). Indeed, the mass spectra revealed a peak at m/z = 209.1 indicating single aldol addition. The $^1$H-NMR spectrum of the sole isolated diastereomer showed a set of doublets at 6.08 and 7.80 ppm for the olefinic protons in α- and β-position, respectively. This is rather unique and in agreement with a series of γ-arylidene-furan-2(5*H*)-ones.[27] The γ-addition is unambiguously confirmed by a cross signal of the methyl group in γ-position ($\mathbf{H}_{Me}$) with the carbon atom of the hydroxymethyl moiety (7-**C**) in the $^1$H,$^{13}$C-HMBC spectra. Obviously, the nucleophilic attack of the anion of **2** (Scheme 2) towards **6** is induced from the γ-position in this case. This is possible according to the Fukui $f^-$ function (Figure 2). The regioselectivity is in clear contrast to the formation of **11**. The aldol addition leads to 5-(hydroxy(*N*-methylimidazol-5-yl)methyl)-5-methylfuran-2(5*H*)-one (**12**) which is free of remaining acidic protons (Scheme 4). Additionally, the methyl group in γ-position prevents condensation towards the corresponding arylidene. It has to be noted, that the reaction is very slow. The yield of 11 % was achieved after several days while extremely slow product precipitation was still ongoing.



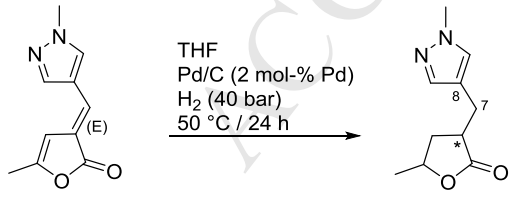

**Scheme 4.** Reaction of *N*-methylimidazole-5-carboxaldehyde (**6**) with α-angelica lactone (**2**) (top) and γ-crotonolactone (**3**) (bottom).

The treatment of γ-crotonolactone (**3**) with **6** revealed a comparable reactivity. The reaction proceeded slightly faster and nucleophilic attack from the γ-position of the anion of **3** towards **6** led to 5-(hydroxy(*N*-methylimidazol-5-yl)methyl)furan-2(5*H*)-one (**13**) in acceptable yields. The structure was readily confirmed as the NMR data are in good agreement with **12**. The protons in α- and β-position show a rather interesting coupling pattern as both are represented by a similar doublet of doublets at 6.19 and 7.74 ppm. This is explained by a virtually identical $^3J_{H,H}$ coupling constant (2.0 Hz) of $\mathbf{H}_\beta$ with $\mathbf{H}_\gamma$ due to the Karplus relation[63] and $^4J_{H,H}$ coupling constant (1.7 Hz) of $\mathbf{H}_\alpha$ with $\mathbf{H}_\gamma$. In contrast to the reaction of aromatic aldehydes with **3** in presence of piperidine reported in literature,[27] the condensation product 5-(*N*-methylimidazol-5-yl)methylene)furan-2(5*H*)-one was not observed. This may be explained by the mild temperature profile applied here. Additionally, and in contrast to **11**, favourable conjugation of the exocyclic double bond with the carbonyl group would be missing in the condensation product. Overall, although the deprotonation of **13** may proceed easily (Scheme 4), neither E1cb elimination nor second aldol addition (explained by the low reactivity of **6** and the anion of **13**) nor rearrangement to the unfavoured non-delocalized tautomer **13b** is observed (Scheme 4).

For the sole isolated diastereomer **13** the question of the *syn*/*anti* configuration preferably formed is of certain interest. For β-hydroxycarbonyl compounds obtained by aldol addition, the chemical shift of the **H**C(OH) proton is often used as indication due to single bond anisotropy. Unfortunately, this can not directly be transferred to the situation of **13**. Straightforward assignment is generally known to be rather prone to error.[64] Furthermore, the NMR data given in literature for similar compounds are contradictory, for example **H**C(OH) of 5-(hydroxy(phenyl)methyl)furan-2(5*H*)-one is reported at 5.09 ppm (*syn*), 4.70 ppm (*anti*)[24] and *vice versa* (5.19 ppm (*anti*), 4.71 ppm (*syn*)[39]). Consequently, we applied the Murata method[64–67] (*J*-based analysis) to elucidate the configuration of **13**. Obtaining good NMR data of **13** was rather challenging since good solvents such as DMSO-$d_6$ led to extremely broad peaks while the

solubility in MeCN-$d_3$ is poor. The NOESY spectra of **13** already gave an indication for the presumable configuration, because only the (*R**/*R**) isomer may satisfy all significant cross signals of the NOESY data (**H**$_\beta$/6-**H**, **Me**$_{Imi}$/6-**H**, **Me**$_{Imi}$/**H**$_\gamma$) while at the same time a cross signal of **Me**$_{Imi}$ and **H**$_{Imi}$ with **H**$_\alpha$ and **H**$_\beta$ is absent at any mixing time (see Figure S1 of the supplementary material for visualization). The resulting geometry is backed by a $^2J_{C,H}$ coupling constant of 6-**H** with **C**$_\gamma$ of 2 Hz measured by Heteronuclear Single Quantum Multiple-Bond Correlation (HSQMBC) as a key step of the *J*-based analysis. The $^2J_{C,H}$ coupling constant follows a Karplus-like relation for the orientation of the **H**-C-**C**$_\gamma$-O dihedral angle.[68] For the given substitution pattern, the geometry assumed from the NOE data with θ(H-C-C-O) roughly between ±135 ° and 180 ° matches the observed coupling constant. Finally, the $^3J_{H,H}$ coupling constant of 6-**H** with **H**$_\gamma$ (5.7 Hz) can be brought in agreement with the structure as well (following the Karplus relation[63] θ(H-C-C-O) = 147 ° is concluded). Overall, this may be seen as a coherent indication for *syn*-configuration of (*R**/*R**)-**13**. Nevertheless, it should be noted that free rotation may lead to wrong interpretation of coupling constants (averaging) and the absence of NOE is not a final proof. The preferred formation of the *syn* diastereomer of **13** is not in accordance with results obtained for the γ-aldol addition of **3** to non-heterocyclic aromatic aldehydes in presence of $NEt_3$. In these cases, a preference (2:1) for the *anti* diastereomer is reported.[34]

The hydrogenation of arylidenedihydrofuranones is a convenient method to achieve functionalized butyrolactones or subsequently tetrahydrofurans from the corresponding furanones.[14] The exocyclic double bond of (*E*)-3-benzylidendihydrofuran-2-one (**8**) is readily reduced with Pd/C at ambient temperature and atmospheric pressure to α-benzyl-γ-butyrolactone.[14] The hydrogenation of α-angelica lactone to γ-valerolactone proceeds at mild conditions as well.[69] Consequently, we investigated the hydrogenation of (*E*)-5-methyl-3-((*N*-methylpyrazol-4-yl)methylene)furan-2(3*H*)-one (**11**). The highly delocalized system unsurprisingly did not show any indication for hydrogenation at moderate conditions. At elevated temperatures, and with alcohols as typical solvent for the Pd-catalyzed hydrogenation, side reactions such as ring-opening were notified. Consequently, dry THF was applied as solvent although a lowering of the catalyst activity must be assumed. Finally, a hydrogen pressure of 40 bar at 50 °C led to complete hydrogenation of **11**. 5-Methyl-3-((*N*-methylpyrazol-4-yl)methyl)dihydrofuran-2-one (**14**) was isolated as racemic mixture within 24 h without the formation of byproducts (Scheme 5).




**11** **14** (83%)

**Scheme 5.** Hydrogenation of **11** to 5-methyl-3-((*N*-methylpyrazol-4-yl)methyl)dihydrofuran-2-one (**14**).

The progress of the reaction is indicated by the vanishing of the yellow colour of the solution. The IR spectra of **14** clearly indicate the loss of delocalization by a shift of the carbonyl vibration from 1748 $cm^{-1}$ (**11**) to 1761 $cm^{-1}$ (**14**). The $^1$H-NMR spectra of **14** show a rather complicate set of signals which is owed to the two sets of diastereotopic protons of **H**$_{\beta,A}$/**H**$_{\beta,B}$ and 7A-**H**/7B-**H** and the corresponding $^2J_{H,H}$ coupling, which allows to assign the structure of **14** unambiguously.

## 3. Conclusion

The aldol reaction of *N*-heterocyclic aldehydes with furan-2-ones had scarcely been investigated before. Applying the same reaction conditions for the aldol reaction of α-angelica lactone (**2**) and γ-crotonolactone (**3**) with 4-pyridinecarboxaldehyde (**4**), *N*-methylpyrazole-4-carboxaldehyde (**5**) and *N*-methylimidazole-5-carboxaldehyde (**6**) in the absence of chelating metal ions, an interesting regioselectivity was resolved. The reactivity can be explained in the context of quantum mechanical reactivity indices. The isolated products were investigated by NMR spectroscopy in detail and the resulting regioisomers have been identified unequivocally. The regioselectivity of the aldol addition has to be dominated by the aldehyde since the anions of **2** and **3** provide comparable nucleophilicity in α- and γ-position. The following observations were made:

- 4-Pyridinecarboxaldehyde (**4**) as highly reactive *N*-heterocyclic aromatic aldehyde leads to subsequent aldol addition alternately in α- and γ-position of **2** and **3** until all acidic protons are replaced.
- *N*-Methylpyrazole-4-carboxaldehyde (**5**) and *N*-methylimidazole-5-carboxaldehyde (**6**) as barely reactive *N*-heterocyclic aromatic aldehydes lead to a single aldol reaction in α- or γ-position, respectively. This is explained by the significantly reduced nucleophilicity of the anion of the first aldol addition product.
- After aldol addition of *N*-methylpyrazole-4-carboxaldehyde (**5**) in α-position of α-angelica lactone (**2**), subsequently immediate condensation to the highly conjugated arylidene takes place.

Overall, the reaction of furan-2-ones with *N*-heterocyclic carbaldehydes offers a convenient way to *N*-donor functionalized lactones. Current work focuses on attempts to exploit the large difference in the reactivity of the carbaldehydes to obtain multiply and differently substituted lactones.

## 4. Experimental section

If not noted differently, all chemicals were bought from *Sigma–Aldrich* and used as received. Diethyl ether and toluene were passed through a PS-MD-4 solvent purification system (*inert technology*) for drying (<10 ppm $H_2O$). 4-Pyridinecarboxaldehyde and benzaldehyde were distilled before use. γ-Butyrolactone (*VWR International GmbH*) was dried over molecular sieve (4 Å) and distilled before use. Furan-2(5*H*)-one and α-angelica lactone (*TCI Europe GmbH*) were distilled before use. Sodium methoxide was freshly prepared from methanol and sodium and dried *in vacuo* before use. Silica gel *60* was used for column chromatography. IR spectra: *Bruker Alpha-T* FT-IR spectrometer (*Bruker Coporation*). For ATR measurements, a Platinum diamond-ATR unit was used. NMR spectra: *Bruker Avance 400* (*Bruker Corporation*) (400 MHz ($^1$H), 100 MHz ($^{13}$C)) and *Avance III 600* (600 MHz ($^1$H), 150 MHz ($^{13}$C)) FT-NMR spectrometer. Chemical shifts are given in ppm relative to tetramethylsilane ($\delta$ = 0.0) or the residual solvent signal of the deuterated solvent. $^2J_{H,C}$ coupling constants have been determined with a pure in phase HSQMBC (pipshsqmbc).[70] Mass spectra: *Varian 320 MS TQ* (*Agilent Technologies*) mass spectrometer at 30 eV and 70 eV for EI mass spectra and for CI mass spectra. *HP 1100 Series* (*Hewlett-Packard*) LC/MS mass spectrometer for ESI mass spectra. For CI, methane was used as ion source gas.

Melting points are uncorrected and were determined with a *Stuart SMP3* apparatus (*Barloworld Scientific Ltd.*).

X-Ray structure analysis for **11** ($C_{10}H_{10}N_2O_2$, $M$ = 190.20 g mol$^{-1}$)**:** A suitable single crystal of **11** was selected under a polarization microscope and mounted in a glass capillary ($d$ = 0.3 mm). The crystal structure was determined by X-ray diffraction analysis using graphite monochromated Mo-$K_\alpha$ radiation (0.71073 Å) [$T$ = 223(2) K], whereas the scattering intensities were collected with a single crystal diffractometer (STOE IPDS II). The crystal structure was solved by Direct Methods using SHELXS-97 and refined using alternating cycles of least squares refinements against $F^2$ (SHELXL-97).[71] All non-H atoms were located in Difference Fourier maps and were refined with anisotropic displacement parameters. The H positions were determined by a final Difference Fourier Synthesis.

**11** crystallized in the monoclinic space group $P2/c$ (no. 14), lattice parameters $a$ = 3.921(1) Å, $b$ = 24.441(6) Å, $c$ = 9.642(3) Å, $\beta$ = 97.10(2)°, $V$ = 916.9(4) Å$^3$, $Z$ = 4, $d_{calc.}$ = 1.378 g cm$^{-3}$, F(000) = 400 using 1575 independent reflections and 168 parameters. $R1$ = 0.0672, $wR2$ = 0.1729 [$I > 2\sigma(I)$], goodness of fit on $F^2$ = 1.111, residual electron density = 0.221 and –0.243 e Å$^{-3}$. Further details of the crystal structure investigations have been deposited with the Cambridge Crystallographic Data Center, CCDC 1542094. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44(1223)-336 033; e-mail: fileserv@ccdc.ac.uk or http://www.ccdc.cam.ac.uk).

All density-functional theory (DFT) calculations were carried out by using the Jaguar 9.1.013[72] software running on Linux 2.6.18-238.el5 SMP (x86_64) on five AMD Phenom II X6 1090T processor workstations (Beowulf-cluster) parallelized with OpenMPI. MM2 optimized structures were used as starting geometries. Complete geometry optimizations were carried out on the LACVP** (Hay-Wadt effective core potential (ECP) basis on heavy atoms, 6-31G** for all other atoms) basis set and with the PBE0 hybrid density functional. All calculated structures were proven to be true minima by the absence of imaginary frequencies. Relative deprotonation energies refer to the deprotonation of γ-butyrolactone in α-position and if appropriate to the (*R*/*R*)-configuration of the protonated species in all cases. Fukui functions $f^-$ were calculated by removal of the fraction of 0.01 electron from the corresponding anion.[58] Plots were obtained using Maestro 10.5.013, the graphical interface of Jaguar. Atomic Fukui indices $f_k$ were calculated from the Mulliken population analysis.[57] Partial charges were obtained with NBO 6.0[73] from the results of the DFT calculations. The global electrophilicity index was calculated[55] by $\omega° = \mu^2/2\eta$ with the electronic chemical potential $\mu = (E_{HOMO}+E_{LUMO})/2$ and the chemical hardness $\eta = E_{LUMO}-E_{HOMO}$ roughly estimated for a comparable series of substances on the same level of theory by Koopmans' theorem.[74,75]

*4.1. (E)-3-Benzylidendihydrofuran-2-one (**8**)*

**8** was synthesized according to literature, but at 0 °C.[14]

$^1$H-NMR (400 MHz, $CDCl_3$): $\delta$ = 3.26 (dt, $J$ = 7.3, 2.8 Hz, 2H, $H_\beta$), 4.47 (t, $J$=7.3 Hz, 2H, $H_\gamma$), 7.39-7.42 (m, 1 H, 10-H), 7.43-7.46 (m, 2H, 9/9'-H), 7.49-7.51 (m, 2H, 8/8'-H), 7.58 (t, $J$ = 2.8 Hz, 1H, 6-H) ppm; (*E*)-configuration has been confirmed by a strong NOE between 8/8'-H and $H_\beta$; $^{13}$C-NMR (100 MHz, $CDCl_3$): $\delta$ = 27.5 (1C, $C_\beta$), 65.4 (1C, $C_\gamma$), 123.5 (1C, $C_\alpha$), 129.0 (2C, 9/9'-C), 129.9 (1C, 10-C), 130.0 (1C, 8/8'-C), 134.7 (1C, 7-C), 136.7 (1C, 6-C), 172.5 (1 C, CO) ppm; EI-MS: *m/z* = 174.1 $[M]^+$ (50), 115.1 $[M - C_2H_2O_2 - H]^+$ (100).

*4.2. General procedure for the reaction of furan-2-ones with N-heterocyclic carbaldehydes*

A solution (0.05 mol-%) of the appropriate furan-2-one (1 eq.) in dry diethyl ether (DEE) was mixed with the *N*-heterocyclic carbaldehyde (1, 2 or 3 eq.) under a nitrogen atmosphere at 0 °C. After stirring for 30 min, excess dry diethylamine (4 eq.) was added dropwise. Stirring was continued for 30 min. The solution was allowed to warm up over night and the product usually precipitated as fluffy powder. The precipitate was washed with cold DEE and dried *in vacuo*.

*4.3. 3,5-Bis(hydroxy(pyridin-4-yl)methyl)-5-methylfuran-2(5H)-one (**9**)*

Following the general procedure, α-angelica lactone (0.92 mL, 1.00 g, 10.19 mmol) and 4-pyridinecarboxaldehyde (1.92 mL, 2.182 g, 20.38 mmol) were used. **9** was obtained as white powder as a mixture of two stereoisomers. Yield: 1.664 g (52 %). Recrystallization from acetone or reversed phase column chromatography (RP-18, MeOH : $CHCl_3$ 1 : 1 v/v, $R_f$ = 0.50) led to one pure isomer. Yield: 0.648 g (20 %). M.p. 178 – 180 °C (decomp.). $^1$H-NMR (600 MHz, DMSO-$d_6$): $\delta$ = 1.46 (s, 3H, Me), 4.78 (d, $J$ = 5.6 Hz, 1H, 7-H), 5.16 (dd, $J$ = 4.6, 1.4 Hz, 1H, 11-H), 6.11 (d, $J$ = 4.6 Hz, 1H, HO-C11), 6.20 (d, $J$ = 5.6 Hz, 1H, HO-C7), 6.93 (m, 2H, 13/13'-H), 7.22 (m, 2H, 9/9'-H), 7.53 (d, $J$ = 1.4 Hz, 1H, $H_\beta$), 8.41-8.42 (m, 4H, 10/10'-H + 14/14'-H) ppm; $^{13}$C-NMR (150 MHz, $CDCl_3$): $\delta$ = 20.5 (1C, Me), 66.3 (1C, 11-C), 74.2 (1C, 7-C), 88.3 (1C, $C_\gamma$), 121.4 (2C, 13/13'-C), 122.5 (2C, 9/9'-C), 135.7 (1C, $C_\alpha$), 148.7 (1C, 8-C), 149.0 (2C, 10/10'-C), 149.4 (2C, 14/14'-C), 150.7 (1C, 12-C), 153.0 (1C, $C_\beta$), 170.5 (1C, CO) ppm; IR (ATR): 3096, 2866, 1743 (CO), 1604, 1462, 1449, 1115, 1004, 804 cm$^{-1}$; ESI-MS: *m/z* = 647.2 $[2M + Na]^+$ (100), 335.0 $[M + Na]^+$ (56), 313.0 $[M + H]^+$ (46); HRMS (ESI): $MH^+$, found 313.1188. $C_{17}H_{17}N_2O_4$ requires 313.1188.

*4.4. 3,5,5-Tris(hydroxy(pyridin-4-yl)methyl)furan-2(5H)-one (**10**)*

Following the general procedure, furan-2(5*H*)-one (0.13 mL, 0.160 g, 1.90 mmol) and 4-pyridinecarboxaldehyde (0.54 mL, 0.612 g, 5.71 mmol) were used. **10** was obtained as white powder and recrystallized from acetone. Yield: 0.668 g (87 %). M.p. 163 – 167 °C (decomp.). $^1$H-NMR (600 MHz, DMSO-$d_6$): $\delta$ = 4.86 (d, $J$ = 5.1 Hz, 1H, 6A-H), 5.11 (dd, $J$ = 5.1, 1.4 Hz, 1H, 10-H), 5.19 (d, $J$ = 5.3 Hz, 1H, 6B-H), 6.09 (d, 5.1 Hz, 1H, HO-C10), 6.28 (d, $J$ = 5.3 Hz, 1H, HO-C6B), 6.34 (d, $J$ = 5.1 Hz, 1H, HO-C6A), 6.80 (dd, $J$ = 4.4, 1.7 Hz, 2H, 12/12'-H), 7.23 (d, $J$ = 1.4 Hz, 1H, $H_\beta$), 7.26 (dd, $J$ = 4.4, 1.7 Hz, 2H, 8A/8A'-H), 7.43 (dd, $J$ = 4.4, 1.7 Hz, 2H, 8B/8B'-H), 8.34 (dd, $J$ = 4.4, 1.7 Hz, 2H, 13/13'-H), 8.39 (dd, $J$ = 4.4, 1.7 Hz, 2H, 9A/9A'-H), 8.57 (dd, $J$ = 4.4, 1.7 Hz, 2H, 9B/9B'-H) ppm; $^{13}$C-NMR (150 MHz, DMSO-$d_6$): $\delta$ = 66.6 (1C, 10-C), 71.2 (1C, 6B-C), 71.3 (1C, 6A-C), 92.4 (1C, $C_\gamma$), 121.4 (2C, 12/12'-C), 122.8 (2C, 8B/8B'-C), 122.8 (2C, 8A/8A'-C), 138.9 (1C, $C_\alpha$), 146.3 (1C, $C_\beta$), 148.3 (1C, 7A-C), 148.6 (1C, 7B-C), 149.0 (2C, 9A/9A'-C), 149.2 (2C, 9B/9B'-C), 149.3 (2C, 13/13'-C), 149.9 (1C, 11-C), 170.3 (1C, CO) ppm; IR (ATR): 3035, 2840, 2708, 1752 (CO), 1604, 1417, 1020, 1006 cm$^{-1}$; ESI-MS: *m/z* = 406.2 $[M + H]^+$ (100), 299.1 [M –HO-CH-py + 2H]$^+$ (15), 281.1 [M –OH –HO-CH-py +H]$^+$ (40); HRMS (ESI): $MH^+$, found 406.1403. $C_{22}H_{20}N_3O_5$ requires 406.1403.

*4.5. (E)-5-Methyl-3-((N-methylpyrazol-4-yl)methylene)furan-2(3H)-one (**11**)*

Following the general procedure, α-angelica lactone (1.85 mL, 2.016 g, 20.55 mmol) and *N*-methylpyrazole-4-carboxaldehyde (2.264 g, 20.55 mmol) were used. **11** was obtained as yellow powder and recrystallized from acetone.

Crystals suitable for X-ray structure determination were obtained from dioxane. Yield: 2.644 g (68 %). M.p. 136 – 138 °C. $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 2.16 (s, 3H, Me), 3.93 (s, 3H, $Me_{pyr}$), 6.04 (s, 1H, $H_\beta$), 7.12 (s, 1H, 7-H), 7.61 (s, 1H, $H_{pyr}$), 7.71 (s, 1H, $H_{pyr}$) ppm; (*E*)-configuration has been confirmed by a strong NOE between both $H_{pyr}$ and $H_\beta$; $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 14.8 (1C, Me), 39.4 (1C, $Me_{pyr}$), 102.2 (1C, $C_\beta$), 118.5 (1C, 8-C), 122.5 (1C, $C_\alpha$), 124.4 (1C, 7-C), 131.7 (1C, $C_{pyr}$), 140.2 (1C, $C_{pyr}$), 156.0 (1C, $C_\gamma$), 170.1 (1C, CO) ppm; IR (ATR): 3120, 3105, 2920, 1748 (CO), 1634, 1622, 1548, 1440, 1013 cm$^{-1}$; ESI-MS: *m/z* = 403.1 $[2M + Na]^+$ (100), 213.0 $[M + Na]^+$ (98). HRMS (ESI): $MH^+$, found 191.0821. $C_{10}H_{11}N_2O_2$ requires 191.0821.

### *4.6. 5-(Hydroxy(N-methylimidazol-5-yl)methyl)-5-methylfuran-2(5H)-one (**12**)*

Following the general procedure, α-angelica lactone (0.61 mL, 0.668 g, 6.81 mmol) and *N*-methylimidazole-5-carboxaldehyde (0.750 g, 6.81 mmol) were used and the mixture was stirred for several days. **12** was obtained as yellow solid and purified by column chromatography (MeCN : MeOH 2 : 1 v/v, $R_f$ = 0.70). Yield: 0.156 g (11 %). M.p. 137 – 139 °C. $^1$H-NMR (600 MHz, MeOD-$d_4$): $\delta$ = 1.51 (s, 3H, Me), 3.71 (s, 3H, $Me_{imi}$), 4.89 (s, 1H, 7-H), 6.08 (d, *J* = 5.7 Hz, 1H, $H_\alpha$), 6.97 (s, 1H, $H_{imi}$), 7.57 (s, 1H, $H_{imi}$), 7.80 (d, *J* = 5.7 Hz, 1H, $H_\beta$) ppm; $^{13}$C-NMR (150 MHz, MeOD-$d_4$): $\delta$ = 19.8 (1C, Me), 32.9 (1C, $Me_{imi}$), 69.9 (1C, 7-C), 92.4 (1C, $C_\gamma$), 122.3 (1C, $C_\alpha$), 128.5 (1C, $C_{imi}$), 131.9 (1C, 8-C), 140.1 (1C, $C_{imi}$), 161.4 (1C, $C_\beta$), 174.5 (1C, CO) ppm; IR (ATR): 3100, 2988, 2824, 2720, 1730 (CO), 1631, 1513, 1376, 1251, 1108, 1043, 817 cm$^{-1}$; ESI-MS: *m/z* = 209.1 $[M + H]^+$ (100); HRMS (ESI): $MH^+$, found 209.0926. $C_{10}H_{13}N_2O_3$ requires 209.0926.

### *4.7. 5-(Hydroxy(N-methylimidazol-5-yl)methyl)furan-2(5H)-one (**13**)*

Following the general procedure, furan-2(5*H*)-one (0.09 mL, 0.104 g, 1.24 mmol) and *N*-methylimidazole-5-carboxaldehyde (0.137 g, 1.24 mmol) were used and the mixture was stirred for several days. **13** was obtained as brown solid and washed several times with chloroform to yield a light brown powder. Yield: 0.118 g (49 %). M.p. 141 – 145 °C (decomp.). $^1$H NMR (600 MHz, MeCN-$d_3$): $\delta$ = 3.65 (s, 3H, $Me_{imi}$), 4.88 (d, J = 5.7 Hz, 1H, 6-H), 5.34 (ddd, *J* = 5.7, 2.0, 1.7 Hz, 1H, $H_\gamma$), 6.19 (dd, *J* = 5.9, 2.0 Hz, 1H, $H_\alpha$), 6.95 (s, 1H, $H_{imi}$), 7.42 (s, 1H, $H_{imi}$), 7.74 (dd, *J* = 5.9, 1.7 Hz, 1 H, $H_\beta$) ppm; $^{13}$C NMR (150 MHz, MeCN-$d_3$): $\delta$ = 32.5 (1C, $Me_{imi}$), 66.2 (1C, 6-C), 85.5 (1C, $C_\gamma$), 123.2 (1C, $C_\alpha$), 128.2 (1C, $C_{imi}$), 131.2 (1C, 7-C), 140.1 (1C, $C_{imi}$), 155.8 (1C, $C_\beta$), 173.7 (1C, CO) ppm; IR (ATR): 3090, 2709, 1753 (CO), 1514, 1170, 1102, 1078, 1035, 830 cm$^{-1}$; ESI-MS: *m/z* = 217.1 $[M + Na]^+$ (100), 195.1 $[M + H]^+$ (85); HRMS (ESI): $MH^+$, found 195.0770. $C_9H_{11}N_2O_3$ requires 195.0770.

### *4.8. 5-Methyl-3-((N-methylpyrazol-4-yl)methyl)dihydrofuran-2-one (**14**)*

A 500 mL lab autoclave (*ROTH Model IV*) was equipped with a solution of (*E*)-5-methyl-3-((*N*-methylpyrazol-4-yl)methylene)furan-2-one (**11**) (0.600 g, 3.16 mmol) in 200 mL dry THF and Pd/C (10% Pd, 0.060 g) was added subsequently. The autoclave was flooded five times with $H_2$ up to a pressure of 5/10/15/20/40 bar. Finally, the autoclave was flooded with $H_2$ at a pressure of 40 bar. The reaction mixture was stirred for 24 h at 50 °C. After completion of the reaction, the suspension was filtered through silica. The solvent was reduced in *vacuo* and the slightly yellow oil purified by column chromatography (EE : PE 9 : 1 v/v, $R_f$ = 0.60). After removal of the solvent, **14** was received as colourless oil. Yield: 0.509 g (83 %). $^1$H NMR (600 MHz, $CDCl_3$): $\delta$ = 1.33 (d, *J* = 6.1 Hz, 3H, Me), 1.55 (ddd, *J* = 12.7, 12.2, 9.4 Hz, 1H, $H_{\beta,A}$), 2.38 (ddd, *J* = 12.7, 8.4, 5.4 Hz, 1H, $H_{\beta,B}$), 2.76 (dd, *J* = 14.2, 7.2 Hz, 1H, 7A-H), 2.80-2.88 (m, 1H, $H_\alpha$), 2.92 (dd, *J* = 14.2, 4.3 Hz, 1H, 7B-H), 3.85 (s, 3H, $Me_{pyr}$), 4.46 (ddq, *J* = 9.4, 8.4, 6.1 Hz, 1H, $H_\gamma$), 7.22 (s, 1H, $H_{pyr}$), 7.30 (s, 1H, $H_{pyr}$) ppm; $^{13}$C NMR (150 MHz, $CDCl_3$): $\delta$ = 21.0 (1 C, Me), 24.4 (1C, 7-C), 35.9 (1C, $C_\beta$), 39.0 (1C, $Me_{pyr}$), 43.0 (1C, $C_\alpha$), 75.3 (1C, $C_\gamma$), 117.4 (1C, 8-C) 129.5 (1C, $C_{pyr}$), 139.4 (1C, $C_{pyr}$), 178.4 (1C, CO); IR (ATR): 2977, 2933, 2890, 1761 (CO), 1387, 1177, 1121, 1018, 986, 955 cm$^{-1}$; ESI-MS: *m/z* = 217.1 $[M + Na]^+$ (100), 195.1 $[M + H]^+$ (10); HRMS (ESI): $MNa^+$, found 217.0962. $C_{10}H_{14}N_2O_2Na$ requires 217.0953.

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## Supplementary Material

Supplementary data containing spectra and details of the DFT calculations can be found at http://dx.doi.org/10.1016/j.tet.2017.

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