Supporting Information

Direct Diels-Alder Reactions of Furfural Derivatives with Maleimides

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General information

Unless stated otherwise, all solvents and commercially available reagents were used as purchased. 2,5-diformylfuran[1] was prepared from 2,5-bishydroxymethylfuran using an aldehyde oxidation procedure described in the literature.[2] 5-methoxymethylfurfural[3] was prepared in two steps by monomethylation of 2,5-bishydroxymethylfuran[4] and subsequent alcohol oxidation.[5] Spectral data was in agreement with literature values.

Nuclear magnetic resonance (NMR) spectra were recorded on an Agilent MRF 400 equipped with a OneNMR probe and Optima Tune system or a Varian VNMR-S-400 equipped with a PFG probe. Resonances were referenced to residual solvent peaks (\[^1\text{H}: \delta 7.26 \text{ ppm}, \; ^{13}\text{C}(\text{^1}\text{H})}: \delta 77.16 \text{ ppm for CDCl}_3, \; ^{1}\text{H}: \delta 2.50 \text{ ppm, } ^{13}\text{C}(\text{^1}\text{H}): \delta 39.52 \text{ ppm for DMSO-d}_6 \text{ and } ^{1}\text{H}: 4.79 \text{ ppm for D}_2\text{O}) Chemical shifts (\(\delta\)) are given in ppm and coupling constants (\(J\)) are quoted in hertz (Hz). Resonances are described as s (singlet), d (doublet), t (triplet), q (quartet), br (broad singlet) and m (multiplet) or combinations thereof. Electrospray Ionization (ESI) mass spectrometry was carried out using an Advion Expression CMS instrument.

Stereochemical information

The \textit{exo}- and \textit{endo}- configurations for the Diels-Alder adducts were assigned in accordance to spectral data available in the literature.[5] Signals \(\text{H}^\text{A}, \text{H}^\text{B}\) and \(\text{H}^\text{C}\) in the adducts are diagnostic: in the \textit{endo} isomer, this pair is deshielded compared to the \textit{exo} isomer; additionally, in accordance to the Karplus equation, coupling between protons \(\text{H}^\text{B}\) and \(\text{H}^\text{C}\) is only observed in the \textit{endo} stereoisomer. These spectral features were consistently noted throughout the series of Diels-Alder adducts synthesized. Furthermore, the dependence of the \textit{exo}/\textit{endo} ratio on time and temperature is consistent with the general theory of Diels-Alder cycloadditions which states that the \textit{exo} isomer is the thermodynamic product and the \textit{endo} isomer is the kinetic product.

Table S1. Diagnostic \(^1\text{H}-\text{NMR signals for the exo/endo pair of Diels-Alder stereoisomers.}

<table>
<thead>
<tr>
<th>R</th>
<th>(\text{H}^\text{A}_{\text{exo}})</th>
<th>(\text{H}^\text{B}_{\text{exo}})</th>
<th>(\text{H}^\text{A}_{\text{endo}})</th>
<th>(\text{H}^\text{B}_{\text{endo}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me (lit.)</td>
<td>2.76 ppm (d, (J = 6.4 \text{ Hz}))</td>
<td>3.02 ppm (d, (J = 6.4 \text{ Hz}))</td>
<td>3.17 ppm (d, (J = 7.6 \text{ Hz}))</td>
<td>3.70 ppm (dd, (J = 7.6, 5.6 \text{ Hz}))</td>
</tr>
<tr>
<td>CH(OH)(_2)</td>
<td>3.16 ppm (d, (J = 6.5 \text{ Hz}))</td>
<td>3.27 ppm (d, (J = 6.5 \text{ Hz}))</td>
<td>3.69 ppm (d, (J = 7.5 \text{ Hz}))</td>
<td>3.86 ppm (dd, (J = 7.5, 5.5 \text{ Hz}))</td>
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</table>
Optimization of reaction conditions

Table S2. Optimization of reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conc</th>
<th>Additive</th>
<th>Temperature</th>
<th>Time</th>
<th>Conversion 1a</th>
<th>exo-3a</th>
<th>endo-3a</th>
<th>Total 3a</th>
</tr>
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<tr>
<td>1</td>
<td>4 M</td>
<td>TFA 20 mol%</td>
<td>60 °C</td>
<td>16 h</td>
<td>52%</td>
<td>36%</td>
<td>10%</td>
<td>46%</td>
</tr>
<tr>
<td>2</td>
<td>2 M</td>
<td>TFA 20 mol%</td>
<td>60 °C</td>
<td>16 h</td>
<td>57%</td>
<td>41%</td>
<td>15%</td>
<td>56%</td>
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<td>TFA 20 mol%</td>
<td>60 °C</td>
<td>16 h</td>
<td>65%</td>
<td>31%</td>
<td>24%</td>
<td>55%</td>
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<td>33%</td>
<td>5%</td>
<td>38%</td>
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<tr>
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<td>2 M</td>
<td>TFA 20 mol%</td>
<td>50 °C</td>
<td>16 h</td>
<td>54%</td>
<td>24%</td>
<td>22%</td>
<td>46%</td>
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<tr>
<td>6</td>
<td>2 M</td>
<td>Sc(OTf)_3 10 mol%</td>
<td>60 °C</td>
<td>16 h</td>
<td>54%</td>
<td>37%</td>
<td>17%</td>
<td>54%</td>
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<td>7</td>
<td>2 M</td>
<td>CBV400 50 mg/mmol</td>
<td>60 °C</td>
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<td>17%</td>
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<td>CBV720 50 mg/mmol</td>
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<td>48%</td>
<td>18%</td>
<td>66%</td>
</tr>
<tr>
<td>9</td>
<td>2 M</td>
<td>NaCl 10 wt-%</td>
<td>60 °C</td>
<td>16 h</td>
<td>53%</td>
<td>37%</td>
<td>16%</td>
<td>53%</td>
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<tr>
<td>10</td>
<td>2 M</td>
<td>NaH_2PO_4 5 wt-%</td>
<td>60 °C</td>
<td>16 h</td>
<td>61%</td>
<td>32%</td>
<td>13%</td>
<td>45%</td>
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<tr>
<td>11</td>
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<td>none</td>
<td>60 °C</td>
<td>16 h</td>
<td>63%</td>
<td>44%</td>
<td>18%</td>
<td>62%</td>
</tr>
<tr>
<td>12</td>
<td>2 M</td>
<td>none</td>
<td>60 °C</td>
<td>41 h</td>
<td>72%</td>
<td>57%</td>
<td>19%</td>
<td>76%</td>
</tr>
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</table>

General procedure: 1a (0.5 mmol), 2a (1.5 equiv) and additive were stirred in water at the indicated temperature for the corresponding amount of time; [a] conversion and yields were determined by crude ¹H-NMR analysis with external standard.

Initially, we experimented with the use of trifluoroacetic acid (TFA) as Brønsted acid catalyst. The effect of concentration was investigated first (entries 1-3); yield was lower in highly concentration solution (4 M). The effect of temperature was then evaluated: higher temperatures led to faster equilibrium, but lower equilibrium conversion (entry 4), while lower temperatures gave a reduced reaction rate (entry 5). Addition of Lewis acid catalyst, zeolites, NaCl or pH buffer did not lead to significantly better results (entries 6-10), with the best performance actually being observed in the absence of any catalyst (entry 11). Finally, prolonging the reaction time led to improved conversion and diastereoselectivity, but the effect was not substantial.

Notably, the exo/endo ratio showed a dependence on concentration, temperature, time and additives; not surprisingly, temperature gave the strongest effect.

As far as we could detect from NMR analysis, conversion of 1a was clean. Hydrolysis of 2a does occur, but to a low extent (typically 2%). This side reaction became more problematic (up to 10%) at elevated temperatures or upon prolonged reaction times; some additives (Sc(OTf)_3, NaH_2PO_4) also promoted 2a hydrolysis.

The role of water was tested by variation of the solvents as shown in Table S3.
Table S3. Solvent screen.

![Chemical structures and reaction equation](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time</th>
<th>exo-3’a</th>
<th>endo-3’a</th>
<th>Total 3’a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>neat</td>
<td>16 h</td>
<td>8%</td>
<td>0%</td>
<td>8%</td>
</tr>
<tr>
<td>2</td>
<td>neat</td>
<td>63 h</td>
<td>10%</td>
<td>0%</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>MeCN</td>
<td>3 h</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>16 h</td>
<td>3%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>5</td>
<td>MeCN</td>
<td>24 h</td>
<td>5%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>6</td>
<td>MeCN</td>
<td>48 h</td>
<td>5%</td>
<td>0%</td>
<td>5%</td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>16 h</td>
<td>2%</td>
<td>0%</td>
<td>2%</td>
</tr>
<tr>
<td>8</td>
<td>CHCl₃</td>
<td>16 h</td>
<td>3%</td>
<td>0%</td>
<td>3%</td>
</tr>
<tr>
<td>9</td>
<td>DMSO</td>
<td>16 h</td>
<td>4%</td>
<td>0%</td>
<td>4%</td>
</tr>
<tr>
<td>10</td>
<td>MeOH</td>
<td>16 h</td>
<td>38%</td>
<td>30%</td>
<td>68%</td>
</tr>
<tr>
<td>11</td>
<td>EtOH</td>
<td>16 h</td>
<td>41%</td>
<td>19%</td>
<td>60%</td>
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<tr>
<td>12</td>
<td>t-BuOH</td>
<td>16 h</td>
<td>2-3%</td>
<td>2-3%</td>
<td>4-6%</td>
</tr>
<tr>
<td>13</td>
<td>TFE</td>
<td>16 h</td>
<td>2-3%</td>
<td>2-3%</td>
<td>4-6%</td>
</tr>
</tbody>
</table>

General procedure: 1a and 2a (1.5 equiv) were stirred in the indicated solvent (2 M) at 60 °C for the amount of time indicated; [a] unless stated otherwise, yields were calculated from the starting material/product ratio determined by crude ¹H-NMR analysis; [b] yields determined by crude ¹H-NMR analysis with external standard; [c] main products were acetals of 3’a; small amount of hemiacetals may be present; [d] due to the low concentration, unambiguous confirmation of product structure was not possible; TFE = 2,2,2-trifluoroethanol.

In nearly all solvents conversions after 16 h were low (<5%). Prolonging the reaction time (MeCN as solvent) did not lead to much improved conversions, suggesting that equilibrium had been reached (e.g. entries 3-6). The highest (equilibrium) conversion was obtained under neat conditions (entry 2). In nucleophilic alcoholic solvent (MeOH, EtOH), conversion of 1a was considerably higher, but in these cases the main products were obtained as acetals; 3’a was not detected. In these solvents, it is possible that the pathway involving furfural acetal has the highest kinetic relevance: in entry 10, 7% of furfural dimethyl acetal was also detected in the crude reaction mixture. In addition, stirring furfural alone in MeOH (2 M, 16 h, 60 °C) afforded 47% acetalization. In non-nucleophilic alcoholic solvents (entries 12 and 13) there was very little conversion and the main products were also most likely formed as acetals.

Experimental procedures

General optimization procedure

2-Furfural 1a (48 mg, 0.5 mmol, 1 equiv) was diluted in demineralized water in a glass vial. N-methyl maleimide 2a (83 mg, 1.5 mmol, 1.5 equiv) and additive were added, the vial was closed and the mixture was heated on oil bath at 60 °C for 16 h. Upon heating, the mixture became homogenous. At the end of the reaction, the mixture was brought to ambient temperature and the conversion and yield of adducts 3a were determined by crude NMR analysis with external standard.
General synthetic procedure A
2-Furfural 1a (4 mmol, 1 equiv) was diluted in demineralized water (2 mL) in a glass vial. Maleimide derivative (6 mmol, 1.5 equiv) was added, the vial was closed and the mixture was heated on oil bath at 60 °C for 16 h. The homogeneity of the mixture depended on the lipophilicity of the maleimide. The solution was then brought to ambient temperature and transferred to a separatory funnel. The aqueous phase was then washed successively with dichloromethane (3x 3 mL) to completely remove unreacted starting materials. The conversion and yield were determined by crude NMR analysis using 1,3,5-trimethoxybenzene for the organic layer and 4-bromopyridine hydrochloride for the aqueous phase.

General synthetic procedure B
5-hydroxymethylfurfural 1b (4 mmol, 1 equiv) was dissolved in demineralized water (2 mL) in a glass vial. Maleimide derivative (6 mmol, 1.5 equiv) was added, the vial was closed and the mixture was heated on oil bath at 60 °C for 16 h. Upon stirring, the mixture gradually became homogenous. The solution was then brought to ambient temperature and transferred to a separatory funnel; solid NaCl was added (400 mg) and dissolved. The aqueous phase was then washed successively with ethyl acetate (4x 8 mL) and dichloromethane (4 mL) to completely remove unreacted starting materials (note that 5-HMF has a high water solubility). The conversion and yield were determined by crude NMR analysis using 1,3,5-trimethoxybenzene for the organic layer and 4-bromopyridine hydrochloride for the aqueous phase.

Scale-up synthesis of 3a (70 mmol)
2-Furfural 1a (6.7 g, 70 mmol, 1 equiv) was diluted in demineralized water (35 mL, 2 M) in a round-bottomed flask. N-methyl maleimide 2a (11.7 g, 105 mmol, 1.5 equiv) was added and the mixture was heated on oil bath at 60 °C for 16 h (closed system). Upon stirring, the mixture gradually became homogenous. The solution was cooled, diluted with dichloromethane (40 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed two more times with dichloromethane (2x 40 mL) to completely remove unreacted starting materials. The conversion and yield were determined by crude NMR analysis using 1,3,5-trimethoxybenzene for the organic layer and 4-bromopyridine hydrochloride for the aqueous phase: 62% furfural conversion, 35% exo-3a, 16% endo-3a, 5% exo-3'a, 1% endo-3'a, 1.5% maleimide hydrolysis to maleic acid.

Recycling experiment
2-Furfural 1a (961 mg, 10 mmol, 1 equiv) was diluted in demineralized water (5 mL, 2 M) in a round-bottomed flask. N-methyl maleimide 2a (1665 g, 15 mmol, 1.5 equiv) was added and the mixture was heated on oil bath at 60 °C for 16 h (closed system). The solution was cooled, diluted with dichloromethane (8 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed two more times with dichloromethane (2x 8 mL) to recover unreacted starting materials. The conversion and yield were determined by crude NMR analysis using 1,3,5-trimethoxybenzene for the organic layer and 4-bromopyridine hydrochloride for the aqueous phase: 41% furfural recovery, 36% exo-3a, 16% endo-3a, 5% exo-3'a, 2% endo-3'a.

The combined organic fractions were concentrated in vacuo. To the resulting mixture water was added (5 mL) and additional 1a (5.2 mmol, 500 mg, 0.52 equiv) and 2a (5.2 mmol, 577 mg, 0.52 equiv). The mixture was again heated on oil bath at 60 °C for 16 h (closed system). The solution was cooled, diluted with dichloromethane (8 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was washed two more times with dichloromethane (2x 8 mL) to completely remove unreacted starting materials. The conversion and yield were determined by crude NMR analysis using 1,3,5-trimethoxybenzene for the organic layer and 4-bromopyridine hydrochloride for the aqueous phase: 38% furfural recovery, 34% exo-3a, 18% endo-3a, 4% exo-3'a, 2% endo-3'a.
**Kinetic experiments**

**2-Furfural 1a**
2-Furfural (192 mg, 2 mmol, 1 equiv) was diluted in D\textsubscript{2}O (2 mL, 1 M) in a glass vial (note that the higher dilution was used to prevent phase separation in the NMR-tube later on). DMSO (27.3 mg) was added as internal standard. *N*-methyl maleimide 2\textsubscript{a} (222 mg, 2 mmol, 1 equiv) was added, the vial was closed and the mixture was heated on oil bath at 60 °C for 100 min until it became homogenous. An NMR sample was then collected and the conversion at 60 °C was monitored by *in situ*-NMR over 60 h.

**5-hydroxymethylfurfural 1b**
5-hydroxymethylfurfural (126 mg, 1 mmol, 1 equiv) was dissolved in D\textsubscript{2}O (0.5 mL, 2 M) in a glass vial. DMSO (22.4 mg) was added as internal standard. *N*-methyl maleimide 2\textsubscript{a} (111 mg, 1 mmol, 1 equiv) was added, the vial was closed and the mixture was heated on oil bath at 60 °C for 10 min until it became homogenous. An NMR sample was then collected and the conversion at 60 °C was monitored by *in situ*-NMR over 60 h.
Computational details
Density functional theory (DFT) calculations were performed using the hybrid PBE0 (PBE1PBE) exchange-correlation functional[6] with all electron 6-311+G(d) basis set on all atoms as implemented in Gaussian 16 C.01 program[7]. Grimme’s D3 correction scheme was used in all calculations[8]. Numerical integration was carried out using the ultrafine grid. Nature of the stationary points was confirmed by the vibrational analysis carried out at the same level of theory. All structures corresponding to local minima showed no imaginary frequencies while transition state (TS) structures were characterized by a single imaginary frequency corresponding to the expected reaction coordinate. Bulk solvent effects were accounted for using the SMD solvation model[9] with standard parameters for water. The effect of specific solvation on the Diels-Alder cycloaddition step was analyzed by introducing 1 or 2 H\textsubscript{2}O molecules in the molecular model; explicit water molecules were found to have minimal impact on the energy barriers. The reaction ($\Delta E_{\text{ZPE}}$) and activation energies ($\Delta E^\ddagger_{\text{ZPE}}$) were corrected for zero-point energy (ZPE) from the normal-mode frequency analysis. Reaction Gibbs free energies ($\Delta G_{\text{THF}}$) and activation Gibbs free energies ($\Delta G^\ddagger_{\text{THF}}$) were computed using the results of the normal-mode analysis within the ideal gas approximation at a pressure of 1 atm and temperature of 298.15 K.

Scheme S1. Reaction path I: the stabilization of the bicycle product of the direct Diels-Alder cycloaddition of furfural and maleimide in water via hydration.

Figure S1. DFT-computed (PBE0-D3/6-311+G(d)/SMD(H\textsubscript{2}O)) ZPE-corrected reaction energy (top) and Gibbs free energy (bottom) diagrams for the reaction path I – hydration stabilization of the Diels-Alder cycloaddition product (dashed line depicts the reaction profile for DA cycloaddition of 1\textsubscript{a} and 2\textsubscript{a} in the absence of the explicit water).
Scheme S2. Reaction path II: the activation of furfural substrate via hydration followed by the Diels-Alder cycloaddition reaction.

Figure S2. DFT-computed (PBE0-D3/6-311+G(d)/SMD(H₂O)) ZPE-corrected reaction energy (top) and Gibbs free energy (bottom) diagrams for the reaction path II - the hydration-promoted Diels-Alder cycloaddition reaction (the effect of the explicit solvation of the reactive complex 1'a···2a with 1 or 2 H₂O molecules is shown with the dashed and dotted energy profiles, respectively).
### Table S4. Computed energies

<table>
<thead>
<tr>
<th>Structure</th>
<th>E</th>
<th>ImFreqs</th>
<th>ZPE</th>
<th>E_ZPE</th>
<th>E_T</th>
<th>H</th>
<th>G</th>
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### Characterization of compounds

**NOTES:**

- the adducts are generally stable in aqueous solution at ambient temperature; nonetheless, as a precaution, they were stored in the fridge; under these conditions, the solutions were generally found stable (no detection of retro-Diels-Alder products) after several months of storage time.
- the adducts could not be isolated from aqueous solution; the retro-Diels-Alder process is facile upon heating (already at 40 °C); freeze drying was not attempted; concentration in vacuo of the solution of hydrogenated adducts B (stable with respect to retro-Diels-Alder reaction) lead to a mixture of diol and oligomeric (polyacetal) species.
- the side products arising from maleimide hydrolysis (maleic acid and amine derivative) remain together with the product in the aqueous layer; spectra also contain signals of residual organic solvent (dichloromethane/ethyl acetate/DMSO) used in the procedure or work-up.
Diels-Alder adduct 3a
Prepared from furfural 1a (384 mg, 4 mmol, 1 equiv) and N-methyl maleimide 2a (666 mg, 6 mmol, 1.5 equiv) according to the general synthetic procedure A.

endo-3a
$^1$H-NMR (D$_2$O, 400 MHz, water suppression): δ 6.53 (dd, J = 6.0 Hz, 1.5 Hz, 1H), 6.49 (d, J = 6.0 Hz, 1H), 5.58 (s, 1H), 5.41 (dd, J = 5.5 Hz, 1.5 Hz, 1H), 3.86 (dd, J = 7.5 Hz, 5.5 Hz, 1H), 3.69 (s, J = 3.0 Hz, 1H) ppm; $^{13}$C($^1$H)-NMR (D$_2$O, 100 MHz): δ 177.8, 177.1, 135.3, 133.7, 93.0, 87.7, 79.1, 47.9, 46.1, 24.4 ppm;

ESI-MS: m/z [M+Na]$^+$ calculated for C$_{10}$H$_{11}$NNaO$_5$: 248.1, found: 248.1.

Diels-Alder adduct 3b
Prepared from furfural 1a (384 mg, 4 mmol, 1 equiv) and maleimide 2b (582, 6 mmol, 1.5 equiv) according to the general synthetic procedure A. Contains small amounts of 2b and unidentified impurities.

endo-3b
$^1$H-NMR (D$_2$O, 400 MHz, water suppression): δ 6.70 (dd, J = 6.0 Hz, 1.5 Hz, 1H), 6.66 (d, J = 6.0 Hz, 1H), 5.44 (s, 1H), 5.32 (d, J = 1.5 Hz, 1H), 3.27 (d, J = 6.5 Hz, 1H), 3.16 (d, J = 6.5 Hz, 1H) ppm; $^{13}$C($^1$H)-NMR (D$_2$O, 100 MHz): δ 179.0, 177.0, 135.3, 133.7, 93.0, 87.7, 81.0, 50.6, 47.8, 24.7 ppm;

ESI-MS: m/z [M+Na]$^+$ calculated for C$_9$H$_9$NNaO$_5$: 234.0, found: 234.1.

Diels-Alder adduct 3c
Prepared from furfural 1a (384 mg, 4 mmol, 1 equiv) and N-ethyl maleimide 2c (750, 6 mmol, 1.5 equiv) according to the general synthetic procedure A.

endo-3c
$^1$H-NMR (D$_2$O, 400 MHz, water suppression): δ 6.55 (dd, J = 6.0 Hz, 1.5 Hz, 1H), 6.50 (d, J = 6.0 Hz, 1H), 5.58 (s, 1H), 5.41 (dd, J = 5.5 Hz, 1.5 Hz, 1H), 3.83 (dd, J = 7.5 Hz, 5.5 Hz, 1H), 3.66 (d, J = 7.5 Hz, 1H), 3.36 (q, J = 7.5 Hz, 2H), 1.00 (t, J = 7.5 Hz, 3H) ppm; $^{13}$C($^1$H)-NMR (D$_2$O, 100 MHz): δ 177.7, 176.9, 135.2, 133.6, 93.1, 87.6, 79.1, 47.7 (overlaps with signal from exo-3c), 45.9, 33.6, 11.6 ppm;
\textsuperscript{1}H-NMR (D\textsubscript{2}O, 400 MHz, water suppression): \(\delta\) 6.69 (dd, \(J = 6.0\) Hz, 1.5 Hz, 1H), 6.65 (d, \(J = 6.0\) Hz, 1H), 5.46 (s, 1H), 5.31 (d, \(J = 1.5\) Hz, 1H), 3.50 (q, \(J = 7.0\) Hz, 2H), 3.25 (d, \(J = 6.5\) Hz, 1H), 3.13 (d, \(J = 6.5\) Hz, 1H), 1.09f (t, \(J = 7.0\) Hz, 3H) ppm; \(\textsuperscript{13}\text{C}{\{\textsuperscript{1}\text{H}\}}\)-NMR (D\textsubscript{2}O, 100 MHz): \(\delta\) 178.9, 176.8, 137.6, 134.8, 92.8, 87.0, 81.0, 50.5, 47.7, 33.9, 11.9 ppm;

ESI-MS: \(m/z\) [M+Na]\textsuperscript{+} calculated for C\textsubscript{11}H\textsubscript{13}NNaO\textsubscript{5}: 262.1, found: 262.0.

Diels-Alder adduct 3d
Prepared from furfural 1a (384 mg, 4 mmol, 1 equiv) and N-propyl maleimide 2d (834 mg, 6 mmol, 1.5 equiv) according to the general synthetic procedure A. Mixture remained biphasic throughout the reaction.

\textbf{endo-3d}
\(\text{H-NMR (D}_2\text{O, 400 MHz, water suppression): } \delta \ 6.57\ (dd, J = 6.0 \text{ Hz, 1.5 Hz, 1H}), 6.52\ (d, J = 6.0 \text{ Hz, 1H}), 5.59\ (s, 1H), 5.41\ (dd, J = 5.5 \text{ Hz, 1.5 Hz, 1H}, \text{ overlaps with signal from exo-3c}), 3.85\ (dd, J = 7.5 \text{ Hz, 5.5 Hz, 1H}), 3.67\ (d, J = 7.5 \text{ Hz, 1H}), 3.29\ (t, J = 7.0 \text{ Hz, 2H}), 1.43\ (sex, J = 7.0 \text{ Hz, 2H}), 0.81\ (t, J = 7.0 \text{ Hz, 3H}) \text{ ppm}; \textsuperscript{13}\text{C}{\{\textsuperscript{1}\text{H}\}}\)-NMR (D\textsubscript{2}O, 100 MHz): \(\delta\) 178.0, 177.2, 135.4, 133.7, 93.1, 87.6, 79.1, 45.9, 40.3, 20.3, 10.6 ppm;

ESI-MS: \(m/z\) [M+Na]\textsuperscript{+} calculated for C\textsubscript{12}H\textsubscript{15}NNaO\textsubscript{5}: 276.1, found: 276.1.

Diels-Alder adduct 3f
Prepared from furfural 1a (384 mg, 4 mmol, 1 equiv) and N-phenyl maleimide 2e (1040 mg, 6 mmol, 1.5 equiv) according to the general synthetic procedure A (DMSO was added as cosolvent, 0.5 mL). Mixture remained biphasic throughout the reaction. The concentration of the adduct 3f was too low to allow characterization.

Diels-Alder adduct 3f
Prepared from 5-HMF 1b (504 mg, 4 mmol, 1 equiv) and N-methyl maleimide 2a (666 mg, 6 mmol, 1.5 equiv) according to the general synthetic procedure B.
ESI-MS: $m/z$ [M+Na]$^+$ calculated for $C_{11}H_{13}NNaO_5$: 278.1, found: 278.0.

Diels-Alder adduct 3g
Prepared from 5-methoxymethyl furfural 1c (140 mg, 1 mmol, 1 equiv) and $N$-methyl maleimide 2a (166 mg, 1.5 mmol, 1.5 equiv) according to the general synthetic procedure A. (DMSO was added as cosolvent, 0.125 mL).

Diels-Alder adduct 3h
Prepared from 5-methyl furfural 1d (440 mg, 4 mmol, 1 equiv) and $N$-methyl maleimide 2a (666 mg, 6 mmol, 1.5 equiv) according to the general synthetic procedure A. (DMSO was added as cosolvent, 0.5 mL).

Diels-Alder adduct 3i
Prepared from 5-bromo furfural 1e (350 mg, 2 mmol, 1 equiv) and $N$-methyl maleimide 2a (333 mg, 3 mmol, 1.5 equiv) according to the general synthetic procedure A. Mixture remained biphasic throughout the reaction.
$^1$H-NMR (D$_2$O, 400 MHz, water suppression): δ 6.61 (d, J = 5.5 Hz, 1H), 6.57 (d, J = 5.5 Hz, 1H), 5.56 (s, 1H, overlaps with signal from exo-$3i$), 4.06 (d, J = 7.5 Hz, 1H), 3.93 (d, J = 7.5 Hz, 1H), 2.84 (s, 3H) ppm; $^{13}$C($^1$H)-NMR (D$_2$O, 100 MHz): δ 175.5, 175.4, 138.9, 135.0, 92.1, 87.0, 86.9, 56.4, 48.7, 24.6 ppm;

exo-$3i$

$^1$H-NMR (D$_2$O, 400 MHz, water suppression): δ 6.76 (d, J = 6.0 Hz, 1H), 6.74 (d, J = 6.0 Hz, 1H), 5.56 (s, 1H, overlaps with signal from endo-$3i$), 3.54 (s, 2H), 3.40 (d, J = 6.0 Hz, 2H), 2.98 (s, 3H) ppm; $^{13}$C($^1$H)-NMR (D$_2$O, 100 MHz): δ 175.2, 175.1, 141.8, 135.9, 91.7, 88.4, 86.3, 54.3, 50.9, 24.9 ppm;

ESI-MS: m/z [M+Na]$^-$ calculated for C$_{10}$H$_{10}$BrNNaO$_5$: 326.0, found: 326.0.

Diels-Alder adduct $3j$
Prepared from diformyl furan $1f$ (248 mg, 2 mmol, 1 equiv) and N-methyl maleimide $2a$ (333 mg, 3 mmol, 1.5 equiv) according to the general synthetic procedure A. (DMSO was added as cosolvent, 0.1 mL). A small amount of (monohydrated) diformylfuran was still present in the aqueous layer.

endo-$3j$

$^1$H-NMR (D$_2$O, 400 MHz, water suppression): δ 6.54 (s, 2H), 5.56 (s, 2H), 3.82 (s, 2H), 2.81 (s, 3H) ppm; $^{13}$C($^1$H)-NMR (D$_2$O, 100 MHz): δ 176.9, 134.6, 92.7, 87.6, 48.3, 24.5 ppm;

Diels-Alder adduct $3k$
Prepared from 5-formyl-2-furoic acid $1g$ (140 mg, 1.0 mmol, 1 equiv) and N-methyl maleimide $2a$ (166 mg, 1.5 mmol, 1.5 equiv) according to the modified general procedure (1 mL water and 0.25 mL DMSO). Upon stirring at 60 °C, the mixture became a solution. After 16 h at 60 °C, the solution was cooled and transferred to a separatory funnel ($1g$ precipitated). The aqueous phase was then washed successively with ethyl acetate (1x 4 mL and 2x 2 mL) and dichloromethane (2x 2 mL) to remove unreacted starting materials. The conversion and yield were determined by crude NMR analysis using 1,3,5-trimethoxybenzene for the organic layer and 4-bromopyridine hydrochloride for the aqueous phase. A small amount of $1g$ was still present in the aqueous layer.

Diels-Alder adduct $3k$
Prepared from 5-formyl-2-furoic acid $1g$ (140 mg, 1.0 mmol, 1 equiv) and N-methyl maleimide $2a$ (166 mg, 1.5 mmol, 1.5 equiv) according to the modified general procedure (1 mL water and 0.25 mL DMSO). Upon stirring at 60 °C, the mixture became a solution. After 16 h at 60 °C, the solution was cooled and transferred to a separatory funnel ($1g$ precipitated). The aqueous phase was then washed successively with ethyl acetate (1x 4 mL and 2x 2 mL) and dichloromethane (2x 2 mL) to remove unreacted starting materials. The conversion and yield were determined by crude NMR analysis using 1,3,5-trimethoxybenzene for the organic layer and 4-bromopyridine hydrochloride for the aqueous phase. A small amount of $1g$ was still present in the aqueous layer.

endo-$3k$

$^1$H-NMR (D$_2$O, 400 MHz, water suppression): δ 6.62 (d, J = 6.0 Hz, 1H), 6.56 (d, J = 6.0 Hz, 1H), 5.56 (s, 1H), 3.85 (d, J = 7.0 Hz, 1H), 3.83 (d, J = 7.0 Hz, 1H), 2.83 (s, 3H) ppm; due to the low concentration of the sample, characterization by $^{13}$C-NMR could not be reliably performed.
1H-NMR (D2O, 400 MHz, water suppression): δ 6.75 (d, J = 6.0 Hz, 1H), 6.73 (d, J = 6.0 Hz, 1H), 5.44 (s, 1H), 3.49 (d, J = 6.5 Hz, 1H), 3.26 (d, J = 6.5 Hz, 1H), 2.94 (s, 3H) ppm; 13C{1H}-NMR (D2O, 100 MHz): δ 181.6, 176.3, 176.3, 138.2, 135.7, 92.3, 90.3, 86.9, 52.9, 49.3, 24.7 ppm.

ESI-MS: m/z [M+Na]+ calculated for C11H11NNaO7: 292.1, found: 292.0.

Diels-Alder adduct 3'i
Prepared from 2-acetyl furfural 1h (440 mg, 4 mmol, 1 equiv) and N-methyl maleimide 2a (666 mg, 6 mmol, 1.5 equiv) according to the general synthetic procedure A. The mixture remained biphasic throughout the reaction. The usual work-up lead to the complete extraction of organics into the dichloromethane layer. A sample of the organic layer (32%) was concentrated in vacuo (at 20-30 °C) and the product was purified by chromatography on silicagel (100% dichloromethane to 3% acetone in dichloromethane). The main product fraction (Rf = 0.26, 3% acetone in dichloromethane) was collected and concentrated in vacuo. A white solid was obtained (92 mg, 32% yield). The solid dissolved much better in CDCl3 than in D2O but characterization in the latter solvent was chosen in order to highlight the ketonic structure of the adduct in aqueous solution.

exo-3'i
1H-NMR (D2O, 400 MHz, water suppression): δ 6.78-6.75 (m, 2H), 5.41 (t, J = 1.0 Hz, 1H), 3.65 (d, J = 6.0 Hz, 1H), 3.30 (d, J = 6.0 Hz, 1H), 2.95 (s, 3H), 2.54 (s, 3H) ppm; 13C{1H}-NMR (D2O, 100 MHz): δ 206.3, 178.2, 176.7, 137.7, 135.0, 94.8, 81.1, 50.4, 49.1, 26.8, 24.6 ppm.

IR (ATR): ν~ = 3097 (w), 3081 (w), 2987 (w), 1770 (w), 1718 (s), 1686 (s), 1439 (m), 1382 (m), 1296 (m), 1055 (m), 899 (m), 732 (m), 655 (w), 597 (w) cm⁻¹.


Diels-Alder adduct exo-3'a
2-Furfural (192 mg, 2 mmol) and N-methyl maleimide (333 mg, 3 mmol) were added to a glass vial. The vial was closed and the mixture was placed on oil bath at 60 °C. The resulting solution was stirred for 63 h. Conversion was determined by crude NMR (10%, exo-3'a detected only). The crude 13C-NMR was also recorded and was consistent with the proposed structure.

exo-3'a
1H-NMR (CDCl3, 400 MHz): δ 9.75 (s, 1H), 6.49 (dd, J = 6.0 Hz, 1.5 Hz, 1H), 6.45 (overlaps with signal from fufural, 1H), 5.20 (d, J = 1.5 Hz, 1H), 3.16 (d, J = 6.5 Hz, 5.5 Hz, 1H), 2.90 (d, J = 6.5 Hz, 1H), 2.77 (s, 3H) ppm; 13C{1H}-NMR (CDCl3, 100 MHz): δ 195.4, 175.0, 173.6, 137.0, 135.0, 94.8, 81.1, 50.2, 48.7, 24.7 ppm.

Diels-Alder adduct exo-3a
2-Furfural (1920 mg, 20 mmol) and N-methyl maleimide (2220 mg, 20 mmol) were added to a glass vial. The vial was closed and the mixture was placed on oil bath at 60 °C. The resulting brown solution was stirred for 120 h. Conversion was determined by crude NMR analysis (9-10%, exo-3'a detected only). The mixture was cooled and subjected to purification by column chromatography on silica gel (100% dichloromethane/5% acetone in dichloromethane/10% acetone in dichloromethane/100% acetone). The main product fraction eluted with 100% acetone (Rf =
0.69 in 100% acetone). Upon concentration *in vacuo* (temperature was not allowed to exceed 30 °C) a brown oil was obtained. Upon standing in air for a few days at ambient temperature, the oil solidified into a brown gum (480 mg) which dissolved poorly in CDCl₃ but readily in D₂O. ¹H-NMR spectrum in D₂O corresponded to exo-3a. ¹H-NMR spectrum in DMSO-d₆ indicated the presence of oligomeric species (likely polycetals). Based on the IR-spectrum, the isolated material features OH groups and no CH=O. The calculated yield (assuming product is fully in geminal diol form) was 10.5%.

IR (ATR): ν̃ = 3600-3000 (br), 1770 (w), 1678 (s), 1437 (m), 1291 (m), 1028 (m), 863 (w), 650 (w), 588 (w) cm⁻¹.

ESI-MS: m/z [M+Na]⁺ calculated for C₁₀H₁₁NNaO₅: 248.1, found: 248.1.

**Hydrazone 4a**
To an aqueous solution of 3a (2 g, 0.87 mmol/g, 1.74 mmol) was added water (2 mL) and N,N-dimethyl hydrazine (132 µL, 1 equiv). The color turned yellow and a precipitate was formed within minutes. The mixture was stirred at ambient temperature for 4 h. The suspension was diluted with water (3 mL) and then filtered; the solids were washed with water (2x 3 mL). The solids were dried *in vacuo*. A yellow powder was obtained (340 mg, 85% yield).

¹H-NMR (DMSO-d₆, 400 MHz): δ 8.08 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 7.64 (t, J = 8.0 Hz, 1H), 7.59 (dd, J = 7.0 Hz, 1.0 Hz, 1H), 3.06 (s, 6H), 3.00 (s, 3H) ppm; ¹³C(¹H)-NMR (DMSO-d₆, 100 MHz): δ 168.7, 167.8, 135.4, 133.6, 132.3, 128.0, 124.2, 123.0, 120.3, 42.2, 23.5 ppm;

IR (ATR): ν̃ = 1759 (m), 1699 (s), 1546 (m), 1438 (m), 1383 (m), 1167 (w), 1070 (m), 1014 (w), 742 (w) cm⁻¹.

ESI-MS: m/z [M+H]⁺ calculated for C₁₂H₁₄N₃O₂: 232.1, found: 232.3.

**Hydrazone 4b**
To an aqueous solution of 3f (1 g, 0.32 mmol) was added N,N-dimethyl hydrazine (29 µL, 1.2 equiv). The color turned yellow and a precipitate was formed within minutes. The mixture was stirred at ambient temperature for 21 h. The suspension was diluted with water (1 mL) and then filtered; the solids were washed with water (1 mL). The solids were dried *in vacuo*. A yellow powder was obtained (72 mg, 86% yield).

¹H-NMR (DMSO-d₆, 400 MHz): δ 8.04 (d, J = 7.5 Hz, 1H), 7.96 (s, 1H), 7.74 (d, J = 7.5 Hz, 1H), 5.39 (t, J = 3.0 Hz, 1H), 4.88 (d, J = 3.0 Hz, 2H), 3.04 (s, 6H), 2.96 (s, 3H) ppm; ¹³C(¹H)-NMR (DMSO-d₆, 100 MHz): δ 168.6, 168.1, 139.5, 133.7, 131.6, 128.0, 126.7, 124.1, 123.6, 58.2, 42.2, 23.4 ppm;

IR (ATR): ν̃ = 3517 (s), 2910 (w), 1754 (m), 1697 (s), 1534 (m), 1443 (m), 1368 (m), 1277 (m), 1080 (s), 1008 (m), 754 (m) cm⁻¹.

ESI-MS: m/z [M+H]⁺ calculated for C₁₃H₁₆N₃O₃: 262.1, found: 262.1.

**Tosyl-hydrazone 5**
To an aqueous solution of 3a (2 g, 0.82 mmol/g, 1.64 mmol) was added ethanol (0.5 mL) and tosyl hydrazine (305 mg, 1 equiv). The mixture was a suspension. The mixture was stirred at ambient temperature for 2.5 h. The suspension was then filtered and the solids were washed with water (3x 1 mL). The solids were dried *in vacuo*. A white powder was obtained (587 mg, 95% yield).
endo-5

H-NMR (DMSO-d6, 400 MHz): 8 11.70 (s, 1H), 7.74 (d, J = 8.0 Hz, 2H), 7.53 (s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 6.47 (dd, J = 5.5 Hz, 1.5 Hz, 1H), 6.42 (d, J = 5.5 Hz, 1H), 5.31 (dd, J = 5.5 Hz, 1.5 Hz, 1H), 3.70 (dd, J = 7.5 Hz, 5.5 Hz, 1H), 3.65 (d, J = 7.5 Hz, 1H), 2.66 (s, 3H), 2.38 (s, 3H) ppm; 13C{1H}-NMR (DMSO-d6, 100 MHz): 8 174.6, 174.0, 143.6, 143.2, 136.0, 135.3, 133.9, 129.7 (overlaps with signal from exo-5), 127.1 (overlaps with signal from exo-5), 88.7, 78.9, 48.4, 47.7, 24.2, 21.0 ppm.

IR (ATR): 8 = 3173 (br), 1766 (w), 1683 (s), 1444 (m), 1292 (m), 1030 (m), 961 (m), 669 (m), 551 (w) cm^{-1}.

ESI-MS: m/z [M+Na]^+ calculated for C_{17}H_{17}N_{3}NaO_{5}S: 398.1, found: 398.1.

Tosyl-hydrazone exo-5

To an aqueous solution of 3a (0.5 g, 0.83 mmol/g, 0.43 mmol) was added CHCl$_3$ (1 mL) and tosyl hydrazine (79 mg, 1 equiv). The mixture was a suspension. The mixture was stirred at ambient temperature for 24 h. The suspension was then filtered and the solids were washed with water. The solids were dried in vacuo. A white powder was obtained (100 mg, 63% yield). NMR analysis indicated that the product was 100% in the exo-configuration.

H-NMR (DMSO-d6, 400 MHz): 8 11.67 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.45 (s, 1H), 7.40 (d, J = 8.0 Hz, 2H), 6.60 (ddd, J = 6.0 Hz, 2.0 Hz, 1.0 Hz, 1H), 6.51 (d, J = 6.0 Hz, 1H), 5.15 (d, J = 2.0 Hz, 1H), 3.10 (d, J = 6.0 Hz, 1H), 3.07 (d, J = 6.0 Hz, 1H), 2.79 (s, 3H), 2.37 (s, 3H) ppm; 13C{1H}-NMR (DMSO-d6, 100 MHz): 8 175.9, 174.4, 143.5, 142.9, 136.9, 136.0, 135.8, 129.7, 127.1, 88.4, 80.7, 50.6, 49.8, 24.5, 21.0 ppm.

IR (ATR): 8 = 3174 (br), 1766 (w), 1683 (s), 1444 (m), 1292 (m), 1029 (m), 961 (m), 551 (w) cm^{-1}.

ESI-MS: m/z [M+Na]^+ calculated for C_{17}H_{17}N_{3}NaO_{5}S: 398.1, found: 398.1.

X-ray structure determination for exo-5 (racemic)

C_{17}H_{17}N_{3}O_{5}S, Fw = 375.39, colorless needle, 0.35 x 0.06 x 0.04 mm$^3$, monoclinic, P2$_1$/n (no. 14), a = 7.1176(2), b = 16.5556(5), c = 14.6211(4) Å, $\beta = 98.965(1)$ °, V = 1701.84(8) Å$^3$, Z = 4, D$_s$ = 1.465 g/cm$^3$, $\mu$ = 0.23 mm$^{-1}$. The diffraction experiment was performed on a Bruker Kappa ApexII diffractometer with sealed tube and Triumph monochromator ($\lambda = 0.71073$ Å) at a temperature of 150(2) K up to a resolution of (sin $\theta$/$\lambda$)$_{max}$ = 0.65 Å$^{-1}$. The Eval15 software$^{[10]}$ was used for the intensity integration. A numerical absorption correction and scaling was performed with SADABS$^{[11]}$ (correction range 0.89-1.00). A total of 38704 reflections was measured, 3904 reflections were unique ($R_{int}$ = 0.041), 3206 reflections were observed ($I > 2\sigma(I)$). The structure was solved with Patterson superposition methods using SHELXT$^{[12]}$. Structure refinement was performed with SHELXL-2018$^{[13]}$ on F$^2$ of all reflections. Non-hydrogen atoms were refined freely with anisotropic displacement parameters. All hydrogen atoms were located in difference Fourier maps. C-H hydrogen atoms were refined with a riding model. The N-H hydrogen atom was refined freely with an isotropic displacement parameter. 249 Parameters were refined with no restraints. R1/wR2 [I > 2\sigma(I)]: 0.0333 / 0.0866. R1/wR2
[all refl.]: 0.0443 / 0.0927. S = 1.033. Residual electron density between -0.32 and 0.35 e/Å³. Geometry calculations and checking for higher symmetry was performed with the PLATON program.\textsuperscript{[14]}

CCDC 2023757 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{fig_s3}
\caption{Displacement ellipsoid plot of exo-5 (50\% probability level).}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{fig_s4}
\caption{One-dimensional hydrogen bonded chain in crystal structure exo-5. C-H hydrogen atoms are omitted for clarity. Symmetry codes $i$: x+\(\frac{1}{2}\), \(\frac{1}{2}\)-y, z-\(\frac{1}{2}\); $ii$: x-\(\frac{1}{2}\), \(\frac{1}{2}\)-y, z+\(\frac{1}{2}\).}
\end{figure}

\begin{table}
\centering
\begin{tabular}{lcc}
\hline
& Bond lengths [Å] & Angles [°] \\
\hline
O3-C2 & 1.4462(16) & & \\
O3-C5 & 1.4483(16) & O3-C2-C10 & 111.20(11) \\
C2-C10 & 1.4898(18) & C2-C10-N2 & 118.19(12) \\
C10-N2 & 1.2701(18) & C10-N2-N3 & 116.28(12) \\
N2-N3 & 1.3878(16) & N2-N3-S1 & 115.91(19) \\
N3-S1 & 1.6481(12) & N2-N3-H3N & 115.91(19) \\
S1-C11 & 1.7565(15) & S1-N3-H3N & 112.8(12) \\
C7-O1 & 1.2161(18) & C2-C10-N2-N3 & 176.31(11) \\
C8-O2 & 1.2088(18) & C10-N2-N3-S1 & 172.80(10) \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\begin{tabular}{lcc}
\hline
& Interactions & Bond lengths [Å] \\
\hline
N3-H3N & H3N…O1$^i$ & N3…O1$^i$ [Å] & N3-H3N…O1$^i$ [°] \\
\hline
\end{tabular}
\end{table}
Symmetry code i: x+½, ½-y, z-½.

Oxime 6
To an aqueous solution of 3a (2 g, 0.79 mmol/g, 1.58 mmol) was added hydroxylamine hydrochloride (114 mg, 1.05 equiv) and 50 wt-% NaOH (131 mg, 1.05 equiv). Water (0.5 mL) was used as rinse. Upon stirring for a few minutes, a white precipitate was observed. The mixture was stirred at ambient temperature for 4 h. The suspension was then filtered and the solids were washed with water (2 x 0.5 mL). The solids were dried in vacuo. A white powder was obtained (241 mg, 69% yield). The NMR indicated the presence of syn/anti isomers. Data below reported only for the major isomers.

endo-6
1H-NMR (DMSO-d6, 400 MHz): δ 11.59 (s, 1H), 7.72 (s, 1H), 6.51-6.45 (m, 2H), 5.33 (dd, J = 5.0 Hz, 1.5 Hz, 1H), 3.75-3.67 (m, 2H), 2.67 (s, 3H) ppm;
13C{1H}-NMR (DMSO-d6, 100 MHz): δ 174.7, 174.3, 144.6, 135.1, 134.3, 87.8, 78.8, 48.4, 47.7, 24.2 ppm;

IR (ATR): ν̃ = 3500-3300 (br), 1771 (w), 1682 (s), 1443 (m), 1386 (w), 1284 (m), 1136 (w), 967 (m), 871 (w), 669 (m), 592 (w) cm⁻¹.

ESI-MS: m/z [M+Na]+ calculated for C₁₀H₁₀N₂NaO₄: 245.1, found: xxx. 245.0.

Carboxylic acid 7
To an aqueous solution of 3a (2 g, 0.82 mmol/g, 1.64 mmol) was added KH₂PO₄ (120 mg) and 35 wt-% H₂O₂ (281 µL, 2 equiv). Solid 80 wt-% NaClO₂ (278 mg, 1.5 equiv) was then added in portions over 1 hour. The solution was stirred at ambient temperature for 18 h. A suspension slowly formed. The mixture was acidified to pH ~ 1 with HCl 4 M, cooled on ice bath and stirred for 1 hour. The suspension was then filtered and rinsed with cold water (0.5 mL). The solids were dried in vacuo. A white powder was obtained (145 mg, 40% yield, 100% exo isomer). The product has a fair solubility in water, which limited the isolated yield.

1H-NMR (DMSO-d6, 400 MHz): δ 6.67 (dd, J = 5.5 Hz, 1.5 Hz, 1H), 6.56 (d, J = 5.5 Hz, 1H), 5.17 (d, J = 1.5 Hz, 1H), 3.16 (d, J = 6.0 Hz, 1H), 3.06 (d, J = 6.0 Hz, 1H), 2.80 (s, 3H) ppm;
13C{1H}-NMR (DMSO-d6, 100 MHz): δ 175.8, 174.2, 167.9, 137.9, 136.4, 88.7, 80.4, 49.9, 48.8, 24.5 ppm;

IR (ATR): ν̃ = 3600-3300 (br), 1769 (w), 1698 (s), 1674 (w), 1445 (m), 1382 (w), 1286 (m), 1062 (m), 867 (w), 656 (m), 591 (w) cm⁻¹.

ESI-MS: m/z [M+Na]+ calculated for C₁₀H₁₀NNaO₅: 246.0, found: 246.1.

Hydrogenated Diels-Alder adduct 8
To an aqueous solution of 3a (2 g, 0.79 mmol/g, 1.58 mmol) was added 10 wt% Pd/C (90 mg). A H₂ balloon was attached and the mixture was stirred at ambient temperature for 1 h. The conversion was checked by NMR and since less than 10% reduction had occurred, a fresh balloon of H₂ was supplied. The mixture was stirred for another hour at ambient temperature.
NMR indicated nearly complete conversion. The solution was filtered over Celite and the filter was washed with water (4x 0.5 mL). The yield, conversion and selectivity were determined by NMR with external standard (4-bromopyridine hydrochloride). Approx. 5% of overreduction of the geminal diol was observed. The yield was 94%.

NMR spectral data

**endo-8**

$^1$H-NMR (D$_2$O, 400 MHz, water suppression): δ 5.38 (s, 1H), 4.95 (t, J = 6.0 Hz, 1H), 3.72 (dd, J = 9.5 Hz, 6.0 Hz, 1H), 3.65 (d, J = 9.5 Hz, 1H), 2.98 (s, 3H), 2.08-1.80 (m, 3H, overlaps with signals from exo-8), 1.75-1.55 (m, 1H, overlaps with signal from exo-8) ppm; $^{13}$C($^1$H)-NMR (D$_2$O, 100 MHz): δ 178.6, 177.7, 90.3, 89.1, 77.7, 52.3, 51.0, 26.4, 26.2, 24.6 ppm;

**exo-8**

$^1$H-NMR (D$_2$O, 400 MHz, water suppression): δ 5.42 (s, 1H), 4.89 (d, J = 5.0 Hz, 1H), 3.32 (d, J = 7.0 Hz, 1H), 3.26 (d, J = 7.0 Hz, 1H), 2.94 (s, 3H), 2.08-1.80 (m, 3H, overlaps with signals from endo-8), 1.75-1.55 (m, 1H, overlaps with signal from endo-8) ppm; $^{13}$C($^1$H)-NMR (D$_2$O, 100 MHz): δ 180.3, 177.9, 89.6, 87.5, 79.4, 51.1, 50.4, 28.3, 26.3, 24.7 ppm;

ESI-MS: m/z [M+Na]$^+$ calculated for C$_{10}$H$_{13}$NNaO$_5$: 250.1, found: 250.1.
Exo-3c

Endo-3c
"Exo-3’a" crude reaction mixture; main signals correspond to unreacted addends.
each diastereoisomer is present as pair of oxime syn/anti isomers
References