1 Details of performing backward search on HMF, 3FO, FF and HBL

The methodology of performing backward search is similar to the forward search and is described in the computational methods section. Here we focused on the backward reaction network of four products, namely hydroxymethylfurfural (HMF), 3-(2H)-furanone (3FO), furfural (FF) and 3-hydroxy-γ-butyrolactone (HBL). Since the reaction mechanisms of FF formation are similar to those of HMF formation, we did not perform an additional exploration for FF, but simply transferred the low barrier reaction patterns discovered in the HMF case study and re-optimized and verified the transition states (TSs).

Backward search from HMF. Starting from HMF, four intermediates were identified with a “backward” free energy of activation ($\Delta G^\dagger_b$) below 45 kcal/mol (node A1-1,A1-2,A1-3, and A1-4 in Fig. S1). Seeding the next step backward search with these four intermediates, three, four, one, and zero new intermediates that satisfied the activation energy criterion (i.e., $\Delta G^\dagger_b < 45$ kcal/mol) were discovered. Among them, intermediate A2-4, A2-5 and A2-6 were also discovered in the forward reaction network (Fig. 1 in the main text). The overall barriers of the conversion
from β-D-Glucose to HMF through intermediates A2-4, A2-5, and A2-6 are 30.98, 32.99, and 34.37 kcal/mol, respectively.

**Backward search from 3FO.** Starting from 3FO, the first step of the backward search discovered four intermediates. One intermediate (node B1-2 in Fig. S2) is also in the forward reaction network. The overall barrier of the conversion from β-D-Glucose to 3FO through this intermediate is 30.98 kcal/mol.

**Backward search from HBL.** The backward search starting from HBL reached out to the maximum depth of four and failed to discover a common intermediate with the forward-reaction network (Fig. S3). This failure indicates that there is no low barrier (i.e. < 40 kcal/mol) reaction pathway converting β-D-Glucose to HBL within the current search scope. However, if removing the activation energy criterion and examining additional channels at
the low-cost GFN2-xTB level of theory, some possible reaction pathways were identified to connect β-D-Glucose with HBL (Fig. S4). For example, the HBL can be formed through sequential retro-aldol ($\Delta G^\ddagger=32.15$ kcal/mol), Korcek cyclization (24.37), β-H elimination (62.60), and a water-catalyzed keto-enol tautomerization (10.80) (red region in Fig. S4). In addition, considering the reactions explored by GFN2-xTB level of theory, it is likely that some bimolecular reactions among intermediates (e.g. formaldehyde, ketene) may lead to HBL formation through relatively low barrier reactions (blue region in Fig. S4).

Figure S3: Backward reaction exploration starting from HBL. After a three-step reaction network exploration, no common intermediates related to the forward reaction network were found.

2 Summary of common reactions mechanisms appearing in the glucose pyrolysis network

Seven reoccurring reaction types in the glucose pyrolysis network are summarized in Figure S5. Reaction “Type a” refers to a hydrogen migration rearrangement, in which two protons transfer between carbonyl and hydroxyl groups. The presence of water as a catalyst
Figure S4: One reaction pathway to the HBL formation with relatively high activation energy (red region). Some additional reaction pathways connecting HBL with intermediates identified in the forward reaction network were obtained from the GNF2-xTB level reaction network (blue region).

has a subtle or even negative effect on reducing the activation energy for this type of reaction. Reaction “Type b” is a ring closure via nucleophilic attack of aldehyde. Because such cyclization reactions serve as the first step of the Korcek mechanism, it is called Korcek cyclization reaction in this work. In this reaction type, the presence of water as a catalyst can reduce the barrier by $\sim 20$ kcal/mol (Fig. S5b). Reaction “Type c” is a common keto-enol tautomerization. As is detailed discussed in the main text section 2.2, a single-water catalyzed mechanism reduces the $\Delta G^\dagger$ by $\sim 30$ kcal/mol, while a combined water- and intermolecular hydroxyl group catalyzed mechanism reduces the $\Delta G^\dagger$ even further. The “Type d” reaction type, $\beta$-H elimination, is a common reaction in hypothesized HMF formation pathways. However, even considering the water catalysis effect, a relatively high barrier over 40 kcal/mol makes it kinetically-irrelevant in the current glucose pyrolysis network. Reaction “Type e” is a retro-aldol reaction, in which a C-C cleavage coupled with a proton transfer forms an aldehyde and an enol. Similar to the hydrogen migration rearrangement, the presence of water as a catalyst does not reduce the $\Delta G^\dagger$. Reaction “Type f” represents a ring closure via electrophilic addition. Although the $\Delta G^\dagger$ of these reactions are relatively high, a dramatic reduction of $\sim 25$ kcal/mol in $\Delta G^\dagger$ by water catalysis makes it an important reaction type in forming key intermediates. The last type of reaction is ring rearrangement, which also plays an important role in the formation of many major products. Taking the
Figure S5: Summary of seven types of reactions that commonly appear in glucose pyrolysis. Transition state geometries and activation energies of water-catalyzed and non-catalyzed reaction mechanisms of each reaction type are provided.

reaction shown in Figure S5g for example, a C-O bond cleavage opens the four-membered ring and then reforms a three-membered ring. In this case, the water-catalyzed mechanism slightly reduces the $\Delta G^\ddagger$ from 29.07 to 26.69 kcal/mol.

3 Summary of important reactions leading to the formation of major products

In this section, we provided a detailed description of important reactions highlighted in the main text (Fig. S6). Reaction a is a ring closure with electrophilic addition catalyzed by
Figure S6: Six important reactions discussed in the main text. “Single cat” and “double cat” refer to whether one or two external water molecules are involved in the reaction mechanisms.

two water molecules. A long distance roaming of a proton from carbon 1 to the α-oxygen of carbon 5 results in 5-membered ring formation. The two water molecules provide a H-transfer network to assist this long distance roaming and reduce the ΔG^† to 29.66 kcal/mol. Starting from a different intermediate, reaction b consists of a shorter distance proton transfer (from the β-H of carbon 2 to the α-oxygen of carbon 1 in Fig. S6b), π-bond rearrangement and a ring closure. Due to the shorter roaming distance, only one water molecule is required to facilitate the proton transfer and the corresponding ΔG^† is 34.37 kcal/mol. The reaction c is the last step of HMF formation, where water elimination from the β-H of carbon 1 and α-hydroxyl group of carbon 5 is coupled with a π-bond rearrangement. With a single water catalyst, the ΔG^† of reaction c is 20.87 kcal/mol. Reaction d is a key step of furfural (FF) formation, involving a proton transfer (from the α-oxygen of carbon 4 to carbon 1) and [1,5] bond shift with a moderate ΔG^† (compared with the rate-limiting step of HMF formation).
of 33.26 kcal/mol. Reactions e and f are the final two steps of 3FO formation. Reaction e is a complex reaction that breaks four bonds (three σ bonds and one π bond) and forms four bonds (one σ bond and three π bonds) through one transition state. With a single water serving as a proton shuttle, this reaction produces three products (water, HAA, and 3-Furanol) with a surprisingly low ΔG‡ of 25.42 kcal/mol. Lastly, reaction f is a double-water catalyzed keto-enol tautomerization with extremely low ΔG‡ (18.60 kcal/mol). Because of the discovery of this reaction, we decided to use the same mechanism for the study of isotopic pathways of HAA formation.

4 Other figures mentioned in the main text

![Figure S7](image_url)  
Figure S7: (a) A summary of kinetically favorable reaction pathways to HAA formation. The labeled carbon atoms reveal how five isotopomers of HAA with carbon indices of (1,2), (2,3), (3,4), (4,5) and (5,6) are formed. (b) Potential energy diagrams with the most favorable reaction pathways to each type of HAA. Different colors correspond to different HAA isotopomer pathways. (c) Illustration of a reaction pathway competing with the formation of (3,4)-HAA. (d) Illustration of two reaction pathways competing with the formation of (2,3)-HAA and (4,5)-HAA.
References