



Figure S3: **Predicted contacts from co-evolutionary analysis** **A.** Scores of predicted contacts from co-evolutionary analysis in decreasing order. The 1500 contacts on the left of the orange dashed line are considered in the text. **B.** Pairwise minimum β -carbon distance matrix (in Å) across all six template structures in Table 2 for the residue positions present in the tobacco aristolochene synthase (TEAS) structure. **C.** The top 1500 predicted co-evolving contacts on the TEAS structure, indicated in black.