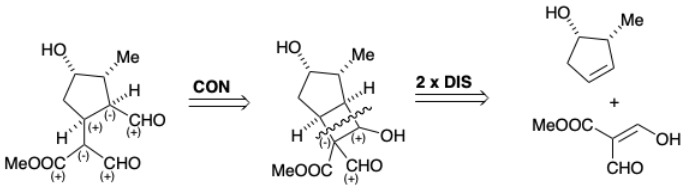
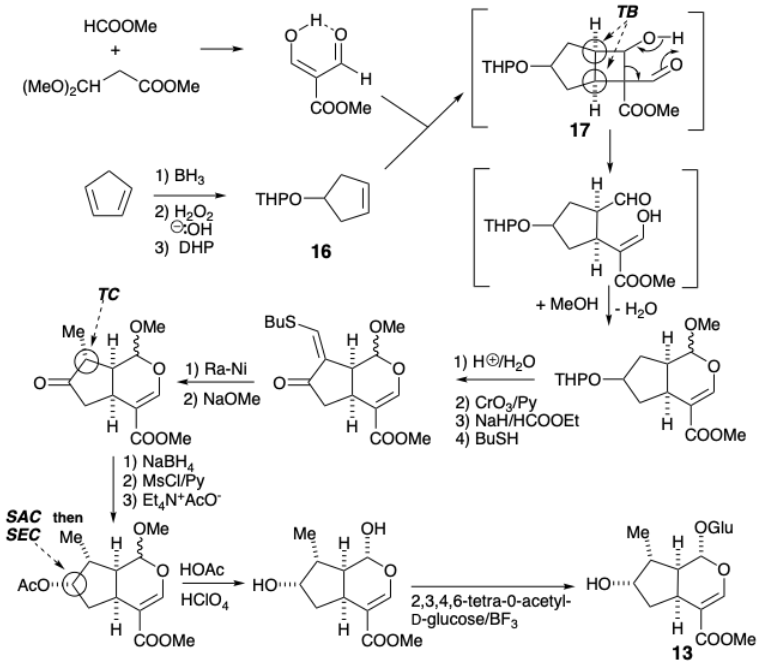
4.2: Syntheses of Loganin

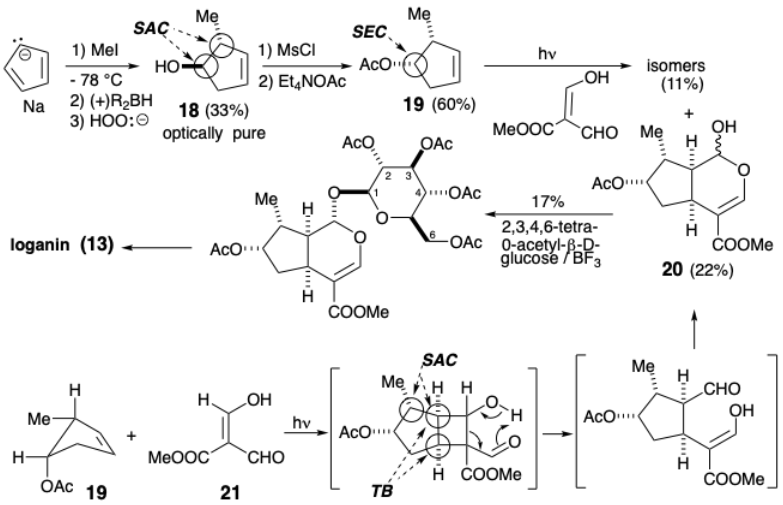
Total syntheses of loganin, that invole polar connection as the first step in the retrosynthetic analysis, have been described. Thus, dislocation of the monocyclic target to a bicyclic target recognizes the potential of retroaldol cleavage of a cyclobutane ring for generation of the required vicinal cis relationship of the malonyl and carboxaldehyde substituents of the target. The cyclobutane can be generated in a two bond-forming cycloaddition process, which, owing to the strain expected for the alternative trans-fused bicyclic product, can be expected to favor the required cis-fused bicyclic intermediate.



Loganin was synthesized in the laboratory by an ingenious scheme involving photochemical cycloaddition to a preformed symmetrical cyclopentene synthon **16**.[1] The desired cis ring fusion is assured by a temporary bridge in the intermediate **17**.



An asymmetric total synthesis of loganin was achieved[2] by an overall strategy for skeletal construction which is similar to, although shorter than, the previous approach. The asymmetric intermediate **18** was produced in high optical purity (at least 98%) by hydroboration of the prochiral symmetrical substrate, 5-methyl-cyclopentadiene, with (+)- or (-)-di-e-pinanylborane.



Since this involves stereospecific addition of the borane to the least hindered face of **18**, the configuration at the carbinol carbon had to be inverted during the preparation of the acetate **19**. The regioselective formation of the isomer **20** results from the steric approach control during the photoannealation. The enol (**21**) attacks the less hindered face of **19**.
