

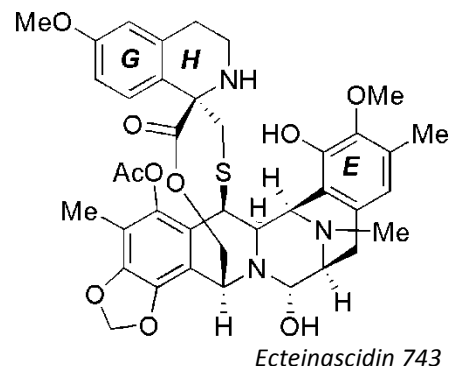
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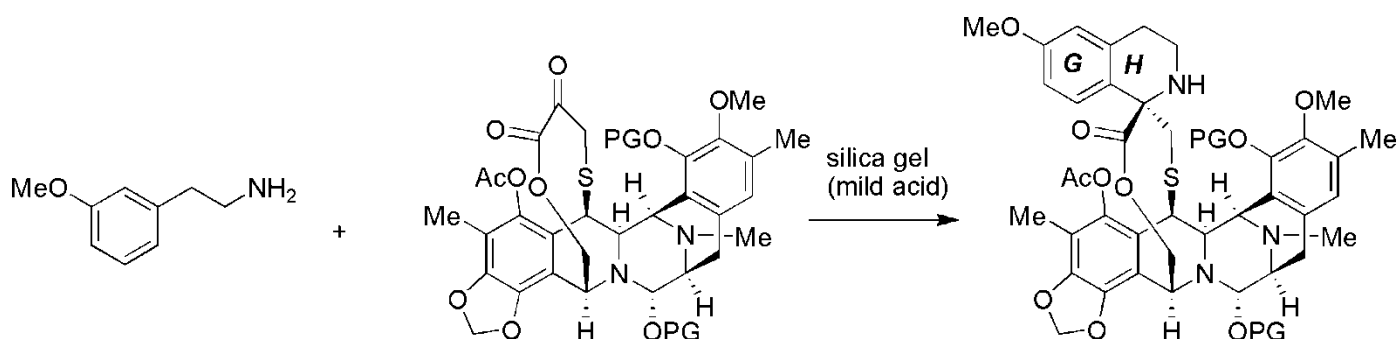
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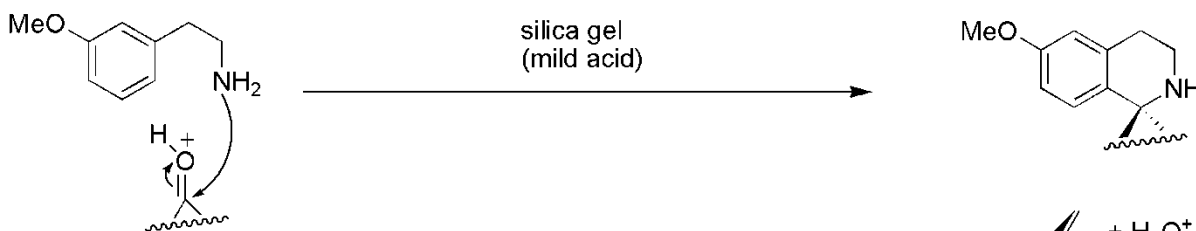
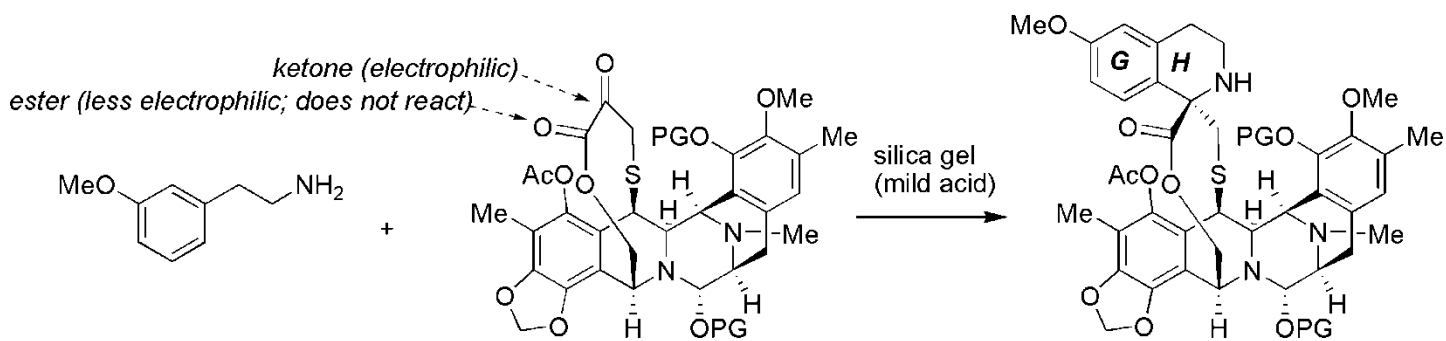
PS #6 – The Pictet-Spengler Reaction, and More Synthetic Planning Practice

Ecteinasidin 743 is a natural product produced by a colorful tunicate (AKA a siphon-feeding sea squirt) that is toxic to predators. Its cancer-cell killing ability was identified by tests of a whole-organism ethanol extract (i.e. “sea squirt in a blender”) in 1972, but its complex structure wasn’t deconvoluted until 1990. *Ect. 743* is so potent that one analysis predicted that a human cancer patient would need only a 5 mg dose to experience curative effects. The Corey group at Harvard completed the synthesis in 1996.

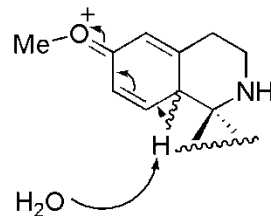
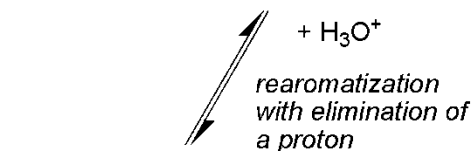
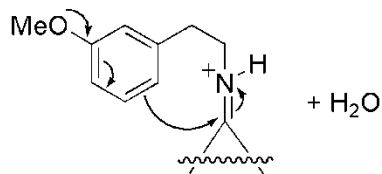
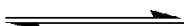
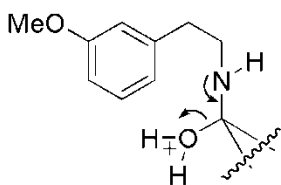
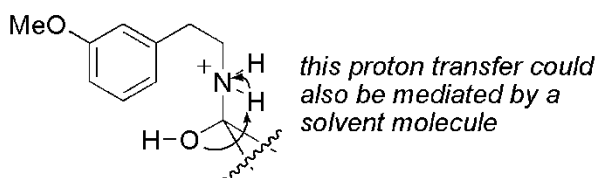


Part A) The **H** ring was formed in the very final stages of the synthesis by the mild and selective reaction shown below. The reaction is called a Pictet-Spengler condensation, and it is mechanistically a close relative of a Mannich reaction. Propose a detailed mechanism for this reaction, explicitly including all proton transfers and intermediates. Abbreviate the structure as needed. (“PG” = “protecting group”; “silica gel” is mildly acidic and always slightly wet, so it can be written as “H₃O⁺”)





first things first: amine + ketone = imine
 (iminium under acid conditions)



iminium is attacked in a Mannich-like manner, except the nucleophile is the electron-rich benzene.

notice that the imine formation takes place without a negatively charged intermediate: protonated ketone is the electrophile, protonated alcohol is the leaving group.

Part B) The E ring building block at right was built up from the commercially available ester at left. Plan a synthesis, showing all intermediates and conditions. Discuss in your group the various protecting groups you might use, and justify your choice(s) in point form.

This alkene would be tough to make using Wittig chemistry because of its substitution. An aldol is a better choice.

