Monday Problem Session – 05/01/09

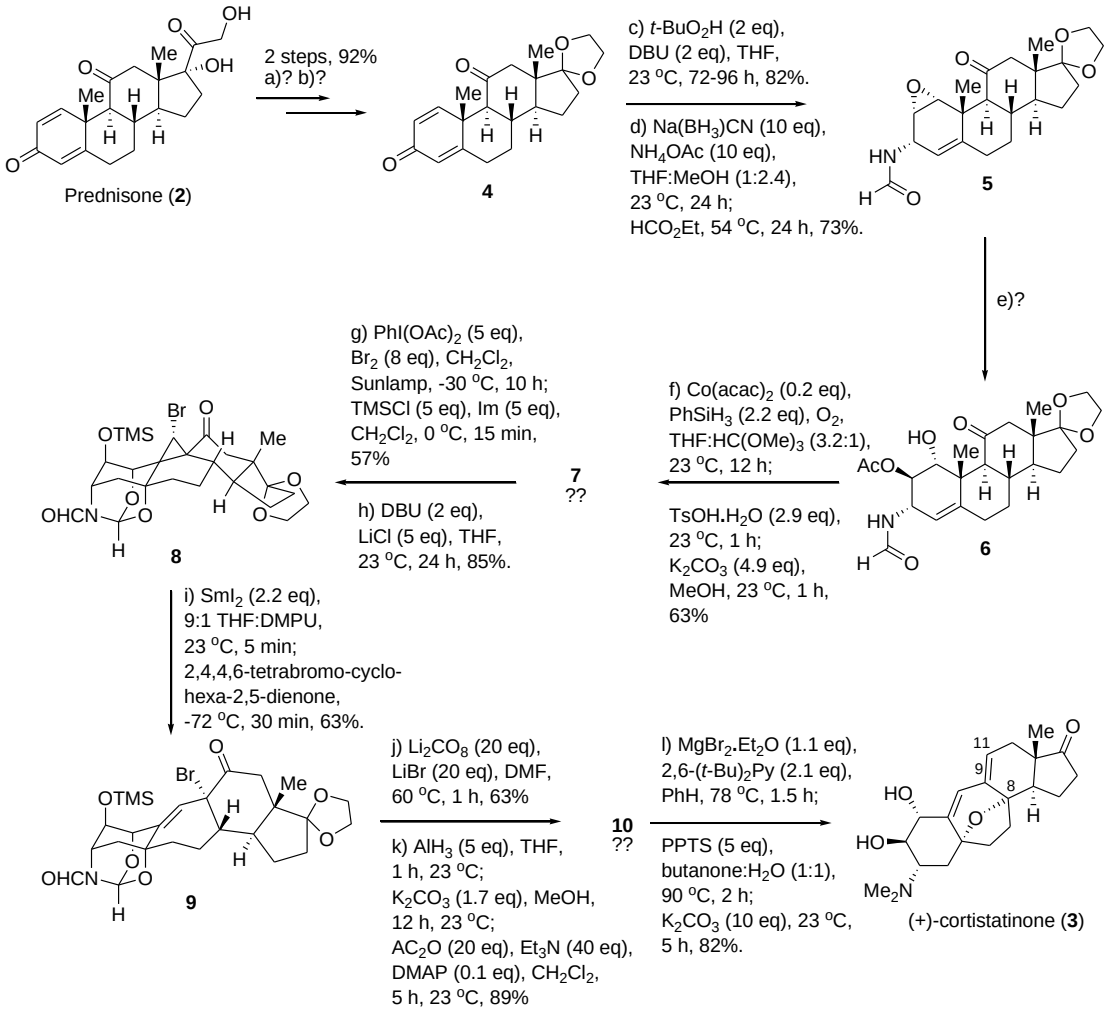
Natural Product Synthesis.

A – Synthesis of (+)-Cortistatin A.[1]

(+)-Cortistatin A (**1**) is the most potent member of the cortistatin family, a small collection of unusual marine alkaloids. This compound inhibits the proliferation of human umbilical vein endothelial cells, with an IC_{50} of 1.8 nM.[1] Due to the unknown biological activity and pharmacological potential of the cortistatin family Baran undertook the synthesis of (+)-cortistatin A (**1**) from commercially available prednisone (**2**)

The first target structure synthesised was (+)-cortistatinone (**3**) (Scheme 1). It was envisaged that straightforward elaboration would allow for the synthesis of (+)-cortistatin A (**1**) as well as the synthesis of other family members.

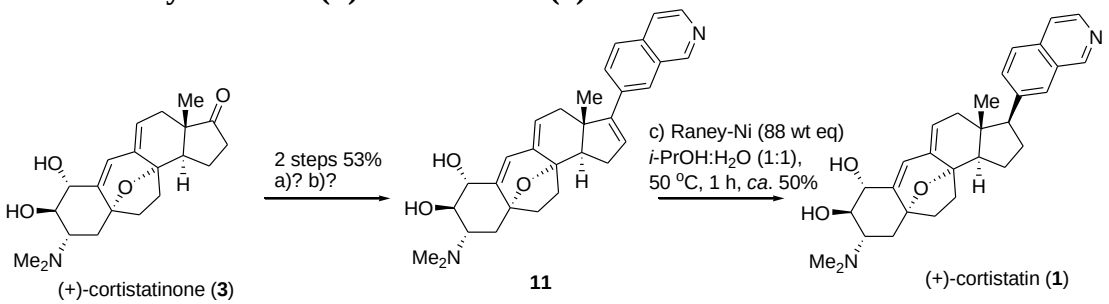
Scheme 1: Synthesis of (+)-cortistatinone (3).



Questions for Scheme 1.

1) Compound **4** was synthesised in two steps from prednisone in 92% after recrystallisation. Suggest reagents and conditions for steps a) and b).
2) The nucleophilic addition to epoxide **5** gave undesired products under both acidic aqueous and basic aqueous conditions. Suggest what the undesired products were and alternative reagents for step e) to give acetate **6**.
3) Compound **7** was synthesised in a one pot synthesis consisting of three steps. Considering the reagents given for step f) give the structure of compound **7**. Give a name for the first reaction in this one pot synthesis.
4) Discuss the mechanism of steps g) and h) to give compound **8**.
5) Discuss the mechanism of step i) to give compound **9**.
6) Given the conditions for steps j) and k) give the structure of compound **10**.
7) Discuss how the acetylation of the C11 alcohol activates the 8,9-olefin towards the conjugate displacement of step l).

Scheme 2: Synthesis of (+)-cortistatin A (1).



Questions for Scheme 2.

1) Suggest reagents and conditions for step a) and b) to form isoquinoline **11**.
2) The final step of the synthesis was a chemoselective reduction with Raney-Ni to give (+)-cortistatin A (**1**). Discuss why this reduction is selective.

References

1. P. S. Baran, *J. Am. Chem. Soc.*, 2008, **130**, 7241.