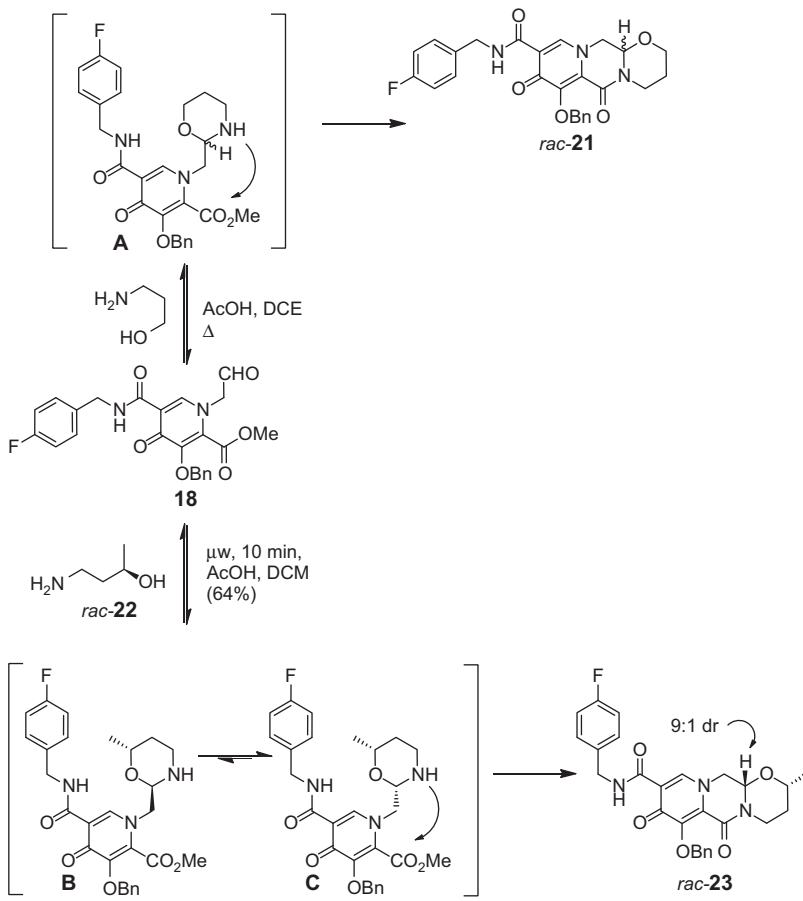
undesirable approach because there was no precedence for our specific system and the fact that our core ring system had limited functional handles on which to append any necessary stereocontrol elements. Consideration of the mechanism for the condensation and ring formation brought to mind the use of substrate control as a possible strategy to establish a handle to impact stereochemistry and also further evaluate SARs. Our hope was that by introducing substitution to the system we would either further improve the biological activity and/or PK and allow for robust stereocontrol or minimally reap the synthetic chemistry benefits and not have any deleterious effects on the above properties. This concept is akin to an auxiliary approach whereby a diastereomeric situation is established to discriminate between isomers, with the exception that, in our case, the auxiliary is retained as a beneficial part of the final drug.

As shown at the top of Scheme 6.2, with the use of an achiral amino alcohol, as had been done for the synthesis of **21**, there is no stereochemical preference



Scheme 6.2 Implementing substrate control of a hemiaminal stereocenter.