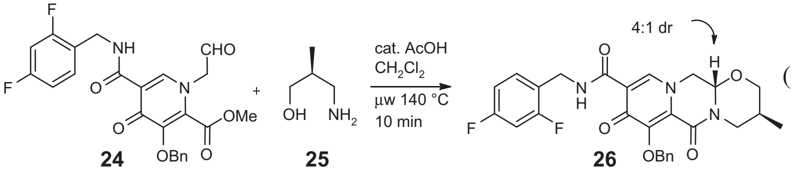
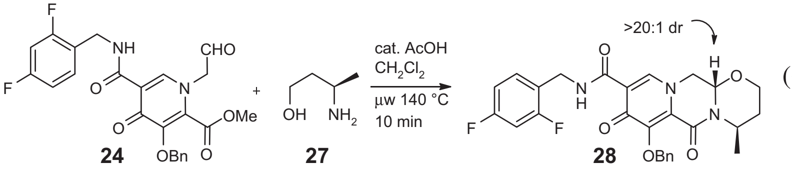
in intermediate **A** and, therefore, racemic product is formed. However, if an amino alcohol with a chiral center is employed, diastereomeric intermediates **B** and **C** are formed, resulting in an equilibrium that should favor the most stable chair conformation, as indicated by intermediate **C**. The final step of lactam ring closure should then lead to a biased product distribution related to the intermediates **B** and **C**. In the first attempt at this method using a racemic alcohol, *rac*-**22**, a 9 : 1 diastereomeric ratio (*dr*) favoring the expected product **23** from having both the methyl and methylene hemiaminal substituent in equatorial orientations was observed. Since our initial experiment was only to prove the relative stereocontrol principle in our system, we immediately repeated the reaction with chiral non-racemic alcohol **22** and obtained enantiomerically pure **23** after removal of the minor diastereomer by achiral silica gel chromatography. Removal of the benzyl ether under standard hydrogenolysis conditions served as a final step to arrive at the desired inhibitor design.

We sought to extend this methodology further to other substituted 1,3-amino alcohols. In the case of the 2-substituted derivative, an erosion of the stereocontrol was observed under the conditions employed to give a still useful 4:1 selectivity [eqn (6.1)]. Placement of the stereocenter next to the amino terminus of the 1,3-amino alcohol led to exceptional diastereoselectivity [eqn 6.2)].



24 **25** **26**

(6.1)



24 **27** **28**

(6.2)

Interestingly, regarding the 3-substituted case shown in eqn (6.2), the stereochemical outcome resulted in the methyl and hydrogen of the two stereocenters existing on the same face, which effectively places the methyl group in an axial position. This may not be expected upon casual inspection of the system since, mechanistically, the reaction is believed to proceed through first formation of the hemiaminal with the aldehyde, which then can cyclize to form the tricyclic-fused amido system. This initial hemiaminal would be expected to exist in the most stable chair form indicated under energy local minima B in Figure 6.8. Ring closure of this would then provide the 1,3-diaxial hydrogen-containing system shown as D in Figure 6.8, but that is not observed.