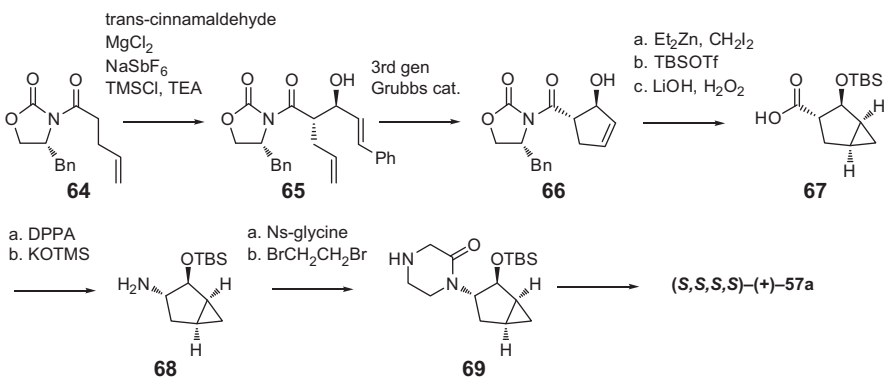
led to the epimerization of the 2-hydroxyl group. Other strong acids, such as TFA and HCl, also promoted epimerization. The inversion appears to occur *via* the cyclic intermediate **58b**, which upon aqueous workup ring opens to give the diastereomeric alcohol **59b**. The corresponding enantiomer **59a** was prepared in an analogous fashion upon treatment of **57a** with TFA. Separately, the cyclic intermediates **58a,b** could be reduced with $NaBH_4$ to afford the piperazine derivatives **60a,b**.

We were able to exploit this serendipitous finding further in the synthesis of another diastereomer (**63a,b**) by epimerizing the alcohol of **61** before installing the cyclopropyl group (via intermediate **62a,b**). Ultimately, we were successful in preparing six of the eight possible stereoisomers.[37]

The low yield for the allylic oxidation of **55** and the need for chiral resolution of the resulting racemic alcohols (±)-**57** necessitated the development of a more efficient synthesis. Utilizing the Evans oxazolidinone (Scheme 5.4), an asymmetric *anti*-aldol reaction between **64** and cinnamaldehyde installed two of the four desired stereocenters with a high diastereomeric ratio (19 : 1) to give **65**.[55] Ring-closing metathesis of the diene **65** with the second generation Grubb's catalyst afforded the cyclopentenol **66** in 94% yield. The hydroxyl-directed cyclopropanation of the olefin, followed by protection of the alcohol and cleavage of the chiral auxiliary, gave intermediate **67** as a single diastereomer. Curtius rearrangement of the carboxylic acid with DPPA and hydrolysis of the isocyanate with KOTMS afforded the amine **68** in 95% yield.[56] The piperazinone was formed in two steps from **68** *via* amide formation with Nosyl-protected glycine followed by alkylation/ring closure with dibromoethane. Removal of the Nosyl group with thiophenol[57] gave **69**, which was subsequently coupled to the pyrazolopyridine acid **45**. The silyl protecting group was removed with TBAF, thereby affording (+)-**57a** as a single isomer in >95% enantiomeric excess. The absolute stereochemistry of (+)-**57a**, was confirmed by single-crystal X-ray crystallography. The 11-step route (from **64**) provided access to >100 g of (+)-**57a** in 33% overall yield.



Scheme 5.4 Asymmetric synthesis of the (*S*,*S*,*S*,*S*)-[3.1.0]bicyclohexan-2-olpiperazinone tail fragment of (+)-**57a**.