Chapter 5

Conclusions and Future Work

5 Conclusions and Future Work

The syntheses of protected APTO ***E*-18** and protected AETD ***E*-30** presented in this thesis are summarised in Figure 5.1. Common intermediate aldehyde **19** was synthesised in thirteen linear steps and 18% overall yield. The stereochemistry of this target was effectively introduced by sequential application of Sharpless AA and AD reactions. Both protected APTO ***E*-18** and protected AETD ***E*-30** were made by olefination of aldehyde **19** with phosphonium salts **20** and **29** respectively. Protected APTO ***E*-18** was synthesised in an overall yield of 11% and this is the first synthesis of a protected form of APTO to date. Protected AETD ***E*-30** was synthesised in an overall yield of 8.3% and this is the second synthesis of a protected form of AETD to date.

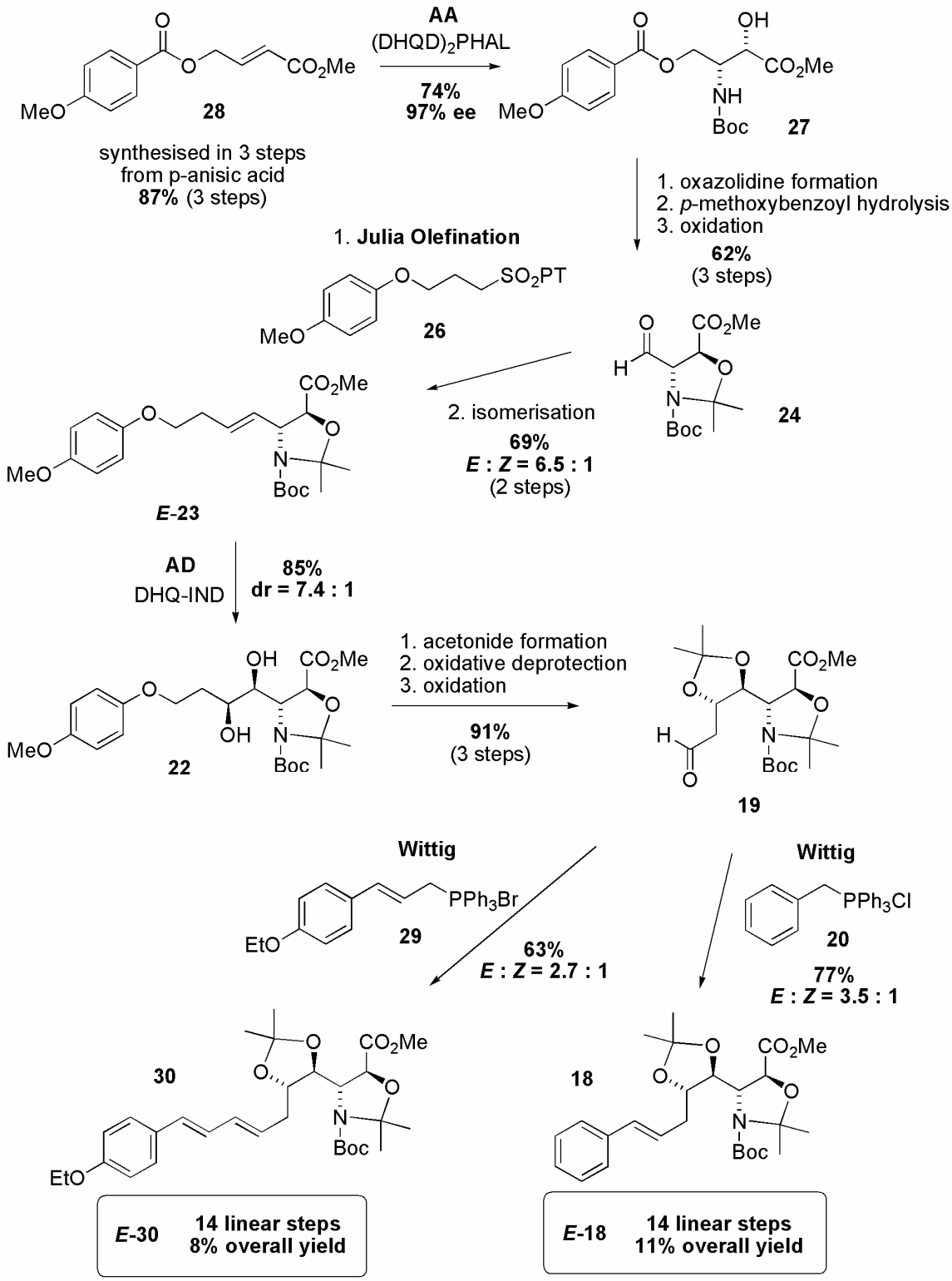

Figure 5.1 Overall syntheses of APTO and AETD.

Direct comparison of this AETD synthesis with the previous synthesis published by Zhu and Ma[24] (see Chapter 1, page **Error! Bookmark not defined.**) is complicated because their strategy involves the coupling of AETD precursor **16**

(Figure 5.2) with a precursor **166** to GABOB, one of the other amino acids in the microsclerodermin, before a two-step oxidation of the C_1-hydroxy to complete the AETD residue **12**. The coupling step was almost quantitative (96%) which makes a yield comparison between protected AETD ***E*-30** and the AETD–GABOB dipeptide **12** appropriate. Zhu and Ma synthesised protected AETD–GABOB dipeptide **12** in twenty one linear steps and 6.1% overall yield. The synthesis presented in this thesis installs the functionality of the compound in fewer steps and a greater overall yield.

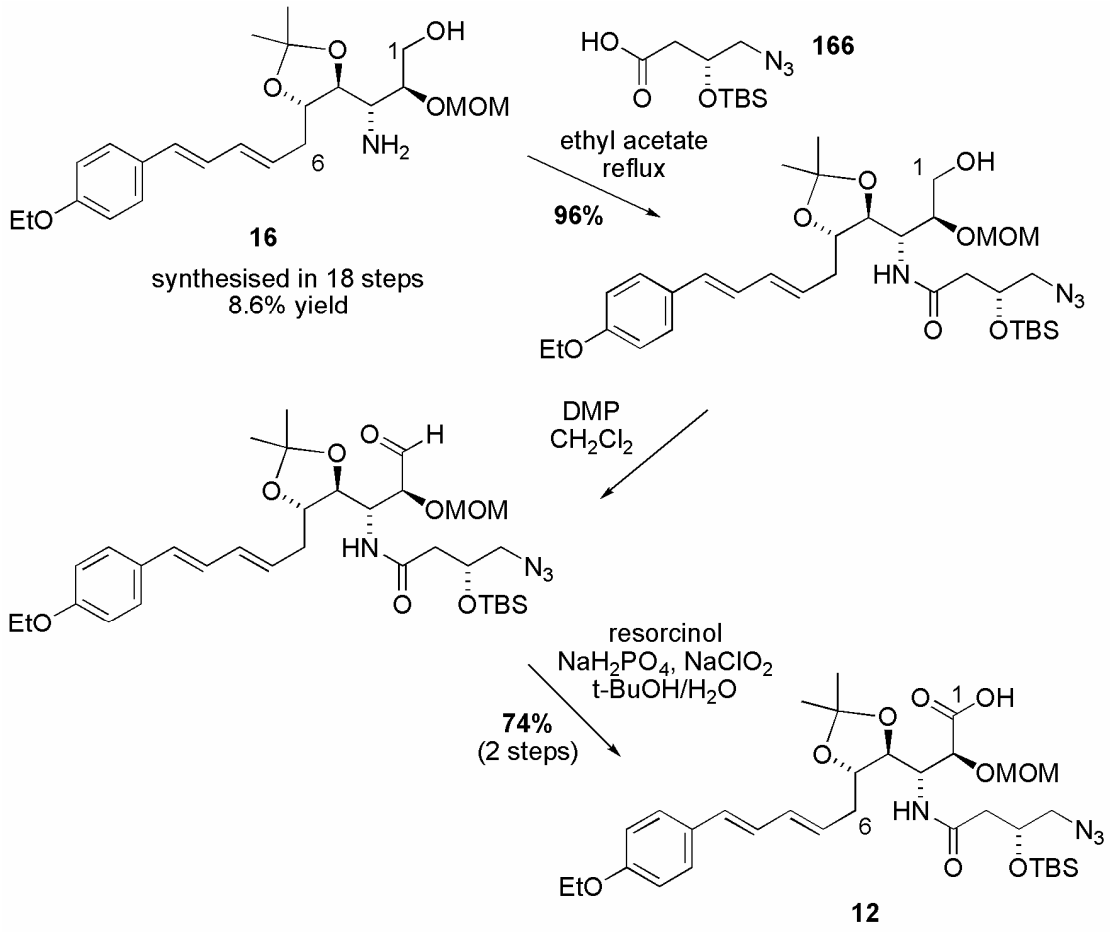

Figure 5.2 Final steps of Zhu and Ma's synthesis.

Initial studies into the application of the synthetic strategy presented in this thesis towards the synthesis of AMPTD have been made (see Chapter 4, page **Error! Bookmark not defined.**). Future studies should involve the completion of this work and the extension to synthesise 10-methyl AMPTD (Figure 5.3). The Julia olefination to reach alkene **32** should be optimised before a study of the AD of alkene ***E*-32**. A dihydroxylation in the absence of a chiral ligand should be

performed to determine the intrinsic diastereofacial selectivity of alkene ***E*-32**. It is hoped that the chiral C_6-methyl will direct the addition to the top face of alkene ***E*-32** as depicted in Figure 5.3 thereby increasing the facial selectivity of the reaction. A ligand study using both pseudo-enantiomeric forms of a range of monomeric ligands should be performed to determine which ligand induces the best selectivity.

An alternative alkene ***E*-167** with a *p*-methoxyphenyl ether protecting group instead of the TBDMS ether in alkene ***E*-32** may improve substrate-catalyst interaction in the AD. Bodkin[36] found that substrates containing a *p*-methoxyphenyl ether group positioned two carbons from the alkene reacted with increased selectivity due to enhanced interaction with the catalyst. It would be interesting to observe any differences in selectivity and reactivity between these two alkenes in the AD reaction. Alkene **167** may be formed with different selectivity in the Julia olefination and should be studied as part of the optimisation of this reaction.

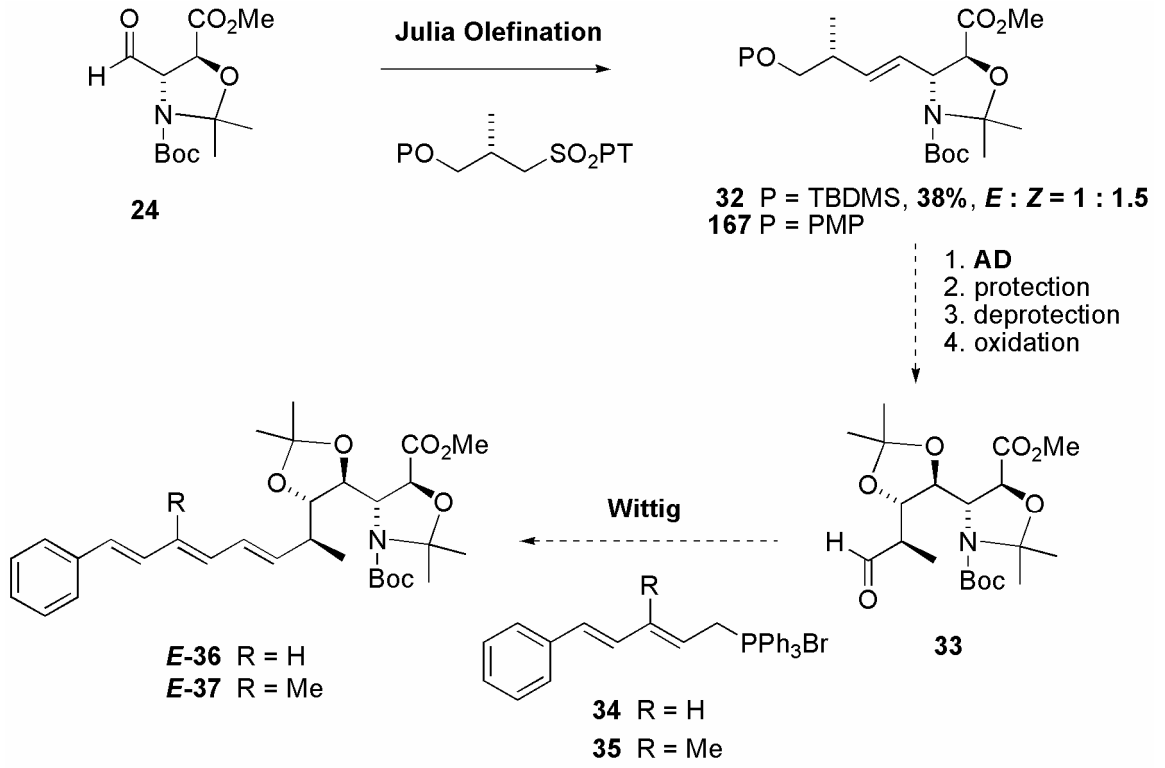

Figure 5.3 Proposed synthesis of AMPTD ***E*-36** and 10-methyl AMPTD ***E*-37**.

Elaboration of the resulting diol to aldehyde **33** should be effected under the same reaction conditions as used to make aldehyde **19**; protection of the diol as

an acetal, de-protection of the C_7-hydroxy protecting group and subsequent oxidation using Dess-Martin periodinane (Figure 5.3). Wittig olefination between aldehyde **33** and phosphonium salt **34** should be used to afford protected AMPTD ***E*-36**. The versatility of the synthesis once again allows simple modification of the final step, incorporating phosphonium salt **35**, to access another analogue 10-methyl AMPTD, ***E*-37**.

Application of the strategy in two possible ways has been proposed to target the final analogue, AMMTD. The first starts from aldehyde **33**, the common late-stage precursor of the AMPTD synthesis. Wittig olefination with unstabilised phosphonium salt **168** should afford alkene **169** with (*Z*)-selectivity (Figure 5.4). Selective hydrogenation of the resulting *Z*-double bond may be used to access protected AMMTD **170**.

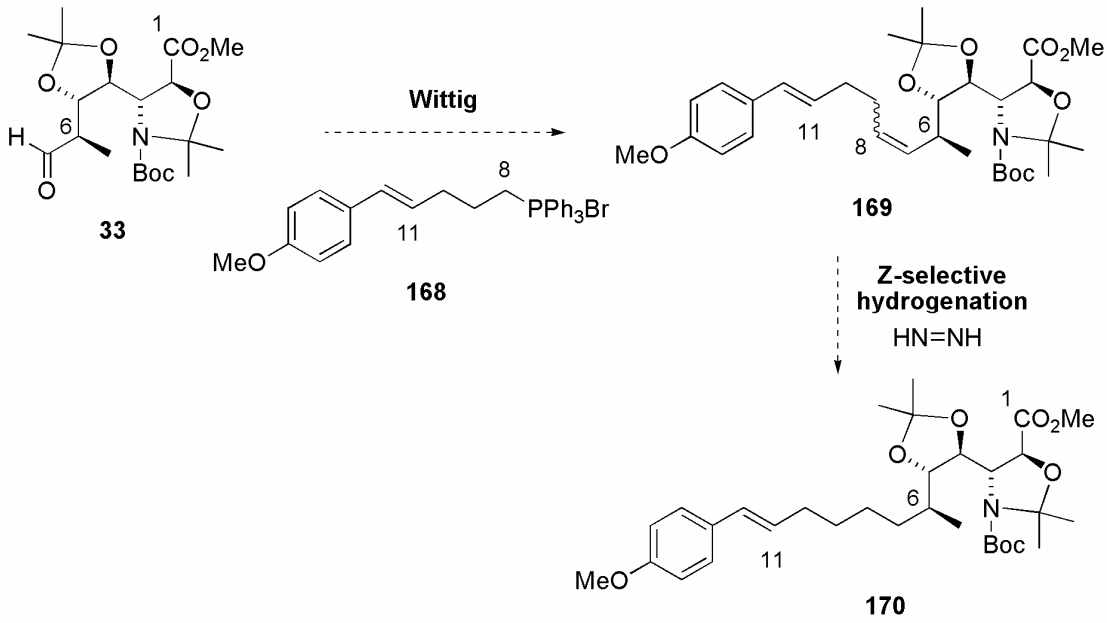

Figure 5.4 First proposed application to AMMTD.

A second approach (Figure 5.5) could involve use of an alternative sulfone **174** in the Julia olefination with aldehyde **24**. Elaboration of the resulting alkene via the same strategy as described previously to afford aldehyde **175** and subsequent olefination with phosphonium salt **176** should afford protected AMMTD **170**.

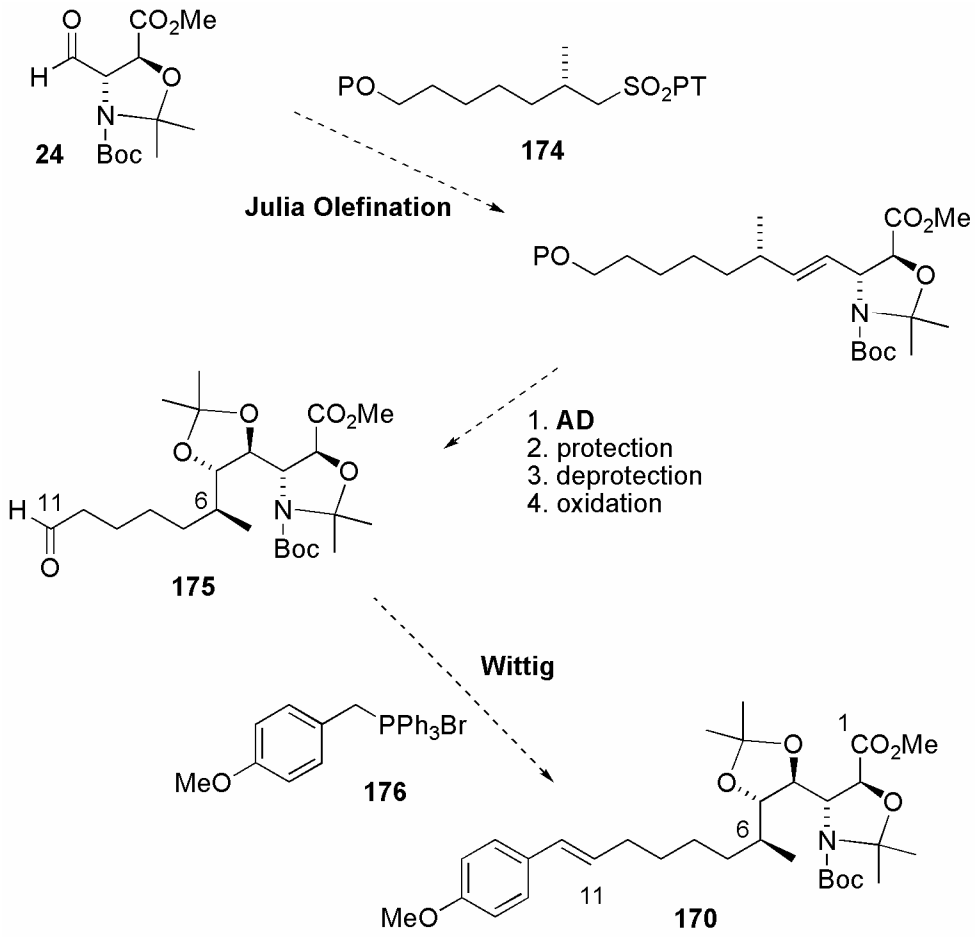

Figure 5.5 Second proposed application to AMMTD.