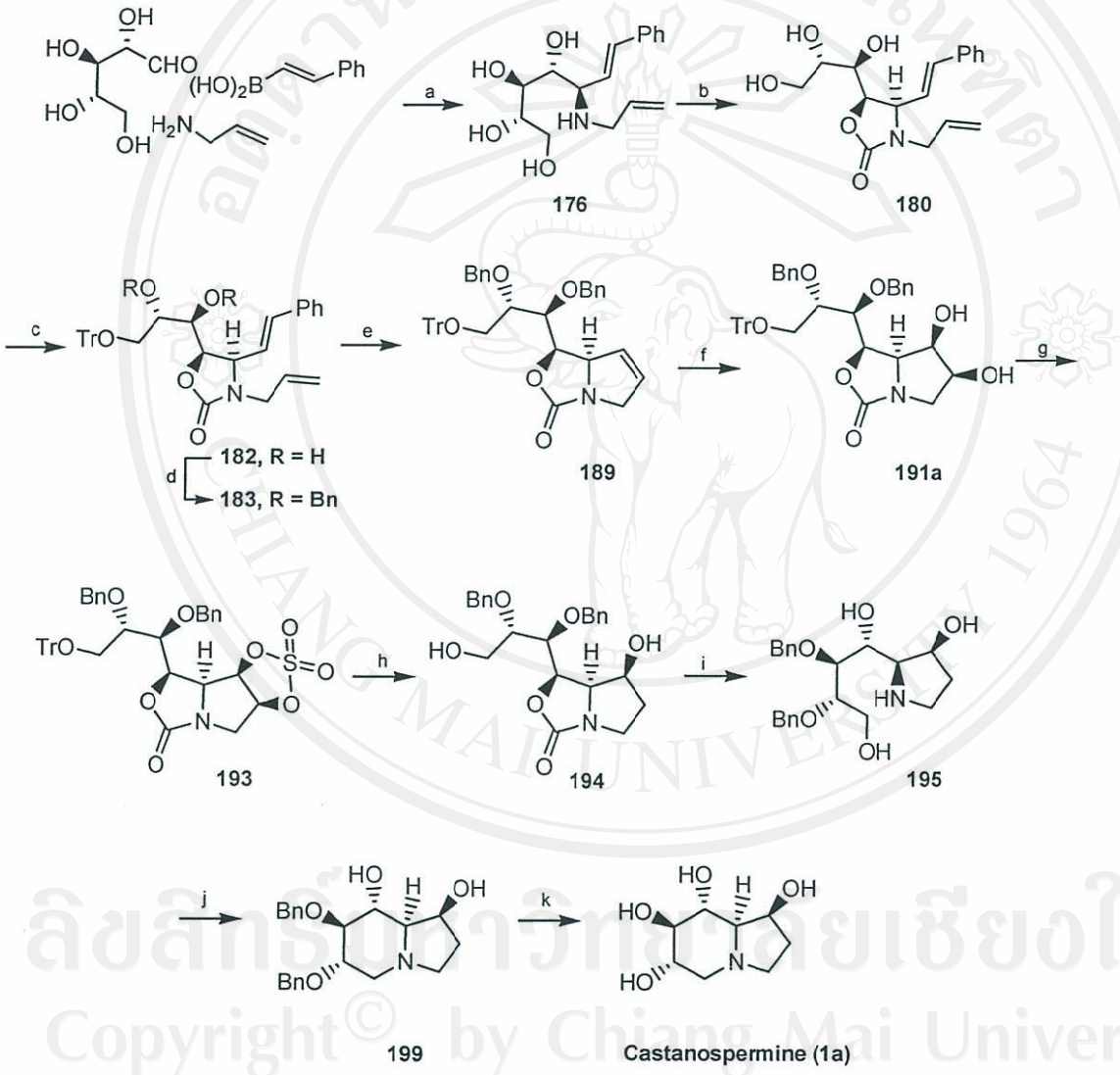
CHAPTER 3

CONCLUSIONS

The aim of this project was to develop a new synthetic strategy for the preparation of castanospermine **1a**. This was achieved by the successful diastereoselective synthesis via the Petasis reaction to condense the three components, L-xylose, allylamine and *trans*-2-phenyl boronic acid which afforded the optically pure β-amino alcohol diene **176** (90% yield). To protect both the amino group and the hydroxyl group at C-4 compound **176** was treated with triphosgene to yield **180** as the major product in a yield of 53%. The three hydroxyl groups of **180** were subsequently protected. The primary hydroxyl was protect by treatment with trityl chloride and the two seconadary hydroxy groups were *O*-benzylated to afforded the major oxazolidinone **183** (56% yield). The key step, the RCM reaction of **183** generated the pyrrolo[1,2-*c*]oxazol-3one **189** (68% yield). *Syn*-dihydroxylation of **189** with OsO_4/NMO gave a mixture of diols **191a** and **191b** in a 83:17 ratio. The mixture was separated employing 2% MeOH/DCM as an eluent on silica gel column. A one pot reaction to form the cyclic sulfate **193** was performed by treatment **191a** with $SOCl_2$/ triethylamine in DCM solution followed by oxidation with $NaIO_4/RuCl_3.3H_2O$ in a mixture of solvents CCl_4:MeCN:H_2O. The cyclic sulfate **193** was treated with $NaBH_4$ in DMAC to open the cyclic sulfate ring at the less hindered position C8a of **193** then acid hydrolysis with H_2SO_4 to give the diol **194** in 63 % yield. The diol **194** was base hydrolyzed with NaOH in MeOH under microwave conditions to give the pyrrolidine triol **195** (80%). Mitsunobu cyclization of **195** was performed by treatment with DIAD/PPh_3 in THF solution to obtain the indolizidine **199** (25%) and two unexpected

cyclized products **196** and **200**. Indolizidine diol **199** was debenzylated with $PdCl_2$ under an atmosphere of H_2 to give the final product, castanospermine **1a**, in an excellent yield (95%) (Scheme 37). Thus castanospermine **1a** was prepared in 11 synthetic steps in 2.0% overall yield from L-xylose.



Scheme 37 ***Reagents and conditions***: (a) EtOH, rt, 48 h, 90%; (b) triphosgene, Et_3N, THF,rt, 24 h, 53%; (c) TrCl, pyridine, rt, 18 h, 87%; (d) NaH, BnBr, *n*-Bu_4NI, THF, rt, 20 h, 56%; (e) Grubbs' II catalyst, DCM, reflux, 24 h, 84%. (f) $K_2OsO_4.2H_2O$, NMO, acetone/water, rt, 20 h, 84%, 83% dr; (g) i. $SOCl_2$, TEA, DCM, rt, 30 min.,

ii. $RuCl_3.3H_2O$, $NaIO_4$, CCl_4:MeCN:H_2O, rt., 3 h., 64%; (h) i. $NaBH_4$, DMAC, rt, 6 h, ii. H_2SO_4 (conc.), H_2O, rt, 48 h, (64%) (i). NaOH, MeOH, H_2O, microwave, 110 °C, 2 h, (80%), (j). DIAD, PPh_3, THF, 0 – 5 °C, 24 h, (25%), $PdCl_2$ (0.08 eq), MeOH, H_2, rt,1 h, (95%).