TABLE OF CONTENTS

	Page
ACKNOWLEDGEMENTS	**iii**
ABSTRACT (ENGLISH)	**iv**
ABSTRACT (THAI)	**viii**
LIST OF TABLES	**xvii**
LIST OF FIGURES	**xviii**
ABBREVIATIONS AND SYMBOLS	**xxi**
PART I ISOLATION OF SOME BIOACTIVE COMPOUNDS FROM *HELIOTROPIUM INDICUM* LINN.	
CHAPTER 1 : INTRODUCTION	2
1.1 Taxa and Classification of *Heliotropium indicum* Linn.	2
1.2 Chemistry of Compounds from *Heliotropium indicum* Linn.	7
1.2.1 Pyrrolizidines	7
1.2.2 Steroids	11
1.2.3 Triterpenoids	13
1.2.4 Flavonoids	14
1.2.5 Miscellaneous Compounds	14
1.3 Biological Activities for the Extracts of *H. indicum*	15
1.4 The Scope and Aims of This Part of Research	16
1.5 Kováts Retention Index Systems	17
CHAPTER 2 : RESULTS AND DISCUSSION	21
2.1 Identification of Essential Oil of *Heliotropium indicum* Linn	21

2.2 Identification of Free Fatty Acids from the Hexane Extract of *H. indicum* 25

CHAPTER 3 : CONCLUSIONS 29

CHAPTER 4 : EXPERIMENTAL 31

4.1 Source and Authentication of the Plant Materials 31

4.2 Analysis of Essential Oil 31

4.3 Extraction and Identification of Fatty Acids 32

4.3.1 Methylation of Fatty Acids 32

4.3.2 GC-FID and GC-MS Analysis 33

4.4 Antituberculosis Activity 34

PART II ASYMMETRIC SYNTHESIS OF (+)-CASTANOSPERMINE

CHAPTER 1 : INTRODUCTION 36

1.1 Indolizidine Alkaloids 37

1.2 Polyhydroxylated Indolizidines 38

1.3 Castanospermine and Stereoisomers 40

1.3.1 Natural Occurrences and Isolation of Castanospermine 41

1.3.2 Biological Activities of Castanospermine 44

1.3.2.1 Enzymology of Glucosidases 46

1.3.2.1.1 Digestive Glucosidases 47

1.3.2.1.2 Lysosomal Glucosidases 49

1.3.2.1.3 Processing α-D-Glucosidases 50

1.3.2.2 Antiviral Activity of Castanospermine 51

1.3.2.3 Anticancer Activity of Castanspermine 53

1.3.2.4 Other Cellular Processes 54

1.3.3 Syntheses of Castanospermine and Its Stereoisomers 56

1.4 Aims of This Project and Proposed Synthetic Approach 86

CHAPTER 2 : RESULTS AND DISCUSSION 88

2.1 Synthesis of (+)-Castanospermine **1a** 88

2.1.1 Synthesis of Pyrrolo[1,2-*c*]oxazol-3-ones 88

2.1.1.1 Petasis Reaction 88

2.1.1.2 Synthesis of Oxazolidinones 90

2.1.1.3 Protections of Hydroxyl Groups 92

2.1.1.4 Ring-Closing Metathesis (RCM) 94

2.1.2 Synthesis of 7*S*-Hydroxypyrrolo[1,2-*c*]oxazol-3-one (**194**) 96

2.1.2.1 *Syn*-Dihydroxylation 96

2.1.2.2 Synthesis of the Cyclic-Sulfate and the Ring Opening 100

2.1.2.3 Deprotection of Oxazolidinone Ring of **194** 102

2.1.3 Mitsunobu Cyclization 104

CHAPTER 3 : CONCLUSIONS 116

CHAPTER 4 : EXPERIMENTAL 119

4.1 General Experimental 119

4.1.1 Nuclear Magnetic Resonance Spectroscopy 119

4.1.2 Chromatography 120

4.1.3 Melting Point 121

4.1.4 Polarimetry 121

4.1.5 Mass Spectrometry 121

4.1.6 Microwave Reactions 121

4.2 Method for the Synthesis of (+)-Castanospermine **1a** 122

4.2.1 (6*E*)-5-(Allylamino)-5,6,7-trideoxy-7-phenyl-D-gluco-hept-6-enitol (**176**) 122

4.2.2 (4*R*,5*R*)-3-Allyl-5-((1*R*,2*S*)-1,2,3-trihydroxypropyl)-4-((*E*)-2-phenylvinyl)-1,3-oxazolidin-2-one (**180**) and (4*R*,5*R*)-3-allyl-5-(((4*S*)-1,3-dioxolan-2-onyl)-hydroxy-methyl)-4-((*Z*)-2-phenylvinyl)-1,3-oxazolidin-2-one (**181**) 123

4.2.3 (4*R*,5*R*)-3-Allyl-5-((1*R*,2*S*)-1,2-dihydroxy-3-(triphenylmethyloxy)-propyl)-4-((*E*)-2-phenylvinyl)-1,3-oxazolidin-2-one (**182**) 126

4.2.4 (4*R*,5*R*)-3-Allyl-5-((1*S*,2*S*)-1,2-bis(benzyloxy)-3-(triphenylmethoxy)-propyl)-4-((*E*)-2-phenylvinyl)-1,3-oxazolidin-2-one (**183**), and (4*R*,5*R*,6*S*)-3-allyl-5-(benzyloxy)-6-((*S*)-1-(benzyloxy)-2-(triphenylmethoxy) ethyl)-4-((*E*)-2-phenylvinyl)-1,3-oxazinan-2-one (**184**). 127

4.2.5 (1*R*,7a*R*)-1-((1*S*,2*S*)-1,2-Bis(benzyloxy)-3-(triphenyl-methoxy)propyl)-1,7a-dihydropyrrolo[1,2-*c*]oxazol-3(5*H*)-one (**189**), and (3*S*,4*R*,4a*R*)-4-(benzyloxy) -3-((*S*)-1-(benzyloxy)-2-(triphenylmethoxy)ethyl)-4,4a-dihydro-3*H*-pyrrolo[1,2-*c*] [1,3]oxazin-1(7*H*)-one (**190**) 130

4.2.6 (1*R*,6*S*,7*R*,7a*R*)-1-((1*S*,2*S*)-1,2-Bis(benzyloxy)-3-

(triphenylmethoxy)propyl)-tetrahydro-6,7-dihydroxypyrrolo[1,2-*c*]oxazol-3(1*H*)-one (**191a**) and (1*R*,6*R*,7*S*,7a*R*)-1-((1*S*,2*S*)-1,2-bis(benzyloxy)-3-(triphenylmethoxy)-propyl)-tetrahydro-6,7-dihydroxypyrrolo[1,2-*c*]oxazol-3 (1*H*)-one (**191b**) 133

4.2.7 (3a*R*, 3b*S*, 4*R*, 8a*S*)-Tetrahydro-4-((1*S*,2*S*)-1,2-bis (benzyloxy)-3-triphenylmethoxy)propyl)-2,2-dioxide,5*H*,4*H*-1,3,2-dioxathiolo[3,4]pyrrolo[1,2-*c*] oxazol-6-one (**193**) 136

4.2.8 (7*S*,7a*R*)-1-((1*S*,2*S*)-1,2-Bis(benzyloxy)-3-hydroxy propyl)tetrahydro-7-hydroxy-pyrrolo[1,2-*c*]oxazol-3(1*H*)-one **(194)** 139

4.2.9 (2*S*,3*S*)-2-((1*R*,2*S*,3*S*)-2,3-Bis(benzyloxy)-1,4-dihydroxybutyl)-pyrrolidin-3-ol (**195**) and (2*R*,3*S*)-2-((2*R*,3*S*,4*S*)-3,4-bis(benzyloxy)-tetrahydrofuran-2-yl)pyrrolidin-3-ol (**196**) 141

4.2.10 (1*S*,6*S*,7*S*,8*R*,8a*S*)-6,7-Bis(benzyloxy)-octahydro indolizine-1,8-diol (**199**) and (3a*S*,6*S*,7*S*,8*R*,8a*S*)-6,7-bis(benzyloxy)-octahydro-1*H*-oxepino-[3,2-*b*] pyrrol-8-ol (**200**) 144

4.2.11 (1*S*,6*S*,7*R*,8*R*,8a*S*)-Octahydroindolizine-1,6,7,8-tetraol (**1a**) 147

REFERENCES 149

VITA 169

LIST OF TABLES

		Page
PART I	**ISOLATION OF SOME BIOACTIVE COMPOUNDS FROM *HELIOTROPIUM INDICUM* LINN.**	
Table 1	Selected ethonomedicinal applications of *H. indicum* in some countries	6
Table 2	Biological activities of the extracts from *H. indicum*	15
Table 3	Volatile components from the aerial part of *H. indicum*	22
Table 4	Chemical components found in the crude hexane extract of *H. indicum* after methylation	26
PART II	**ASYMMETRIC SYNTHESIS OF (+)-CASTANOSPERMINE**	
Table 5	Reagents and results of attempted oxazolidinones formation	91
Table 6	Reagents and results of epoxidation of the alkene **189**	97
Table 7	Physical and ^{1}H NMR spectral data for the natural (+)-castanospermine, the synthetic (+)-castanospermine **1a** and the authentic (+)-castanospermine (Phytex)	114
Table 8	^{13}C NMR spectral data for natural (+)-castanospermine, the synthetic (+)-castanospermine **1a** and an authentic sample of (+)-castanospermine (Phytex)	115

LIST OF FIGURES

		Page
PART I	**ISOLATION OF SOME BIOACTIVE COMPOUNDS FROM *HELIOTROPIUM INDICUM* LINN.**	
Figure 1	The inflorescence of *Heliotropium indicum* Linn	3
Figure 2	Gas chromatogram of the essential oil of *H. indicum.*	21
Figure 3	The structures of some identified components of the essential oil	24
Figure 4	TIC profile of the methylated crude hexane extract from the aerial parts of *H. indicum.*	25
PART II	**ASYMMETRIC SYNTHESIS OF (+)-CASTANOSPERMINE**	
Figure 5	Structure and stereochemistry of (+)-castanospermine (**1a**)	36
Figure 6	The parent structures of bicyclic of indolizidine alkaloids	37
Figure 7	Representative examples of glycosidase inhibitors with the structure of polyhydroxylated indolizidines	39
Figure 8	Structures of (+)-castanospermine (**1a**) and its synthesized epimers	40
Figure 9	Structure of deoxynorjirimycin (**5**) and DMDP (**6**)	41
Figure 10	Distribution areas of *C. australe* in Australia	42
Figure 11	Pictures of the leaves, inflorescences and seeds of *C. australe*	43

Figure 12	**A)** Coordination of reducing agent (M-H) with intermediate **A** **B)** Favored direction of hydrogen transfer due to steric group (NHBoc) in **B**	63
Figure 13	The model of the favor (A) and disfavor (B) chelating of aldehyde **78** and AcOEt in the presence of Li-complex	69
Figure 14	Possible mechanism of the formation of β-amino alcohol diene **176** via the boronate complex intermediate **A**	96
Figure 15	Reaction mechanism of triphosgene and oxazolidinone **180** to form dioxalanoyl oxazolidinone **181**	91
Figure 16	Chemical shifts of CH-5 and CH-1' in oxazolidinone **183** and CH-5 and CH-6 in oxazinanone **184**	94
Figure 17	Molecular Model (PC Spartan Pro AM1) of **189**	99
Figure 18	Molecular Model (PC Spartan Pro AM1) of **191a** and NOESY correlation of H-6, H-7 and H7a)	100
Figure 19	Mechanism of cyclic-sulfate ring opening by the hydride ion from $NaBH_4$	102
Figure 20	The two possibility pathways to generate the side product **196** by base hydrolysis under microwave reaction	103
Figure 21	HMBC correlations of the compound **196**	108
Figure 22	^1H NMR spectrum (500 MHz, CD_3OD) of compound **199**	109
Figure 23	^{13}C NMR spectrum (500 MHz, CD_3OD) of compound **199**	110
Figure 24	^1H NMR spectrum (500 MHz, D_2O) of authetic (+)-castanospermine from Phytex, Australia	111

Figure 25 ^{1}H NMR spectrum (500 MHz, D_2O) of synthetic (+)-castanospermine **1a** 112

Figure 26 ^{1}H NMR spectrum (300 MHz, D_2O) of (+)-castanospermine, which was published in the journal *Phytochemistry* by Hohenschutz *et al.* 112

Figure 27 ^{13}C NMR spectrum (125 MHz, D_2O) of authentic (+)-castanospermine from Phytex, Australia 113

Figure 28 ^{13}C NMR spectrum (125 MHz, D_2O) of synthetic (+)-castanospermine **1a** 113

ABBREVIATIONS AND SYMBOLS

$[\alpha]_D$	specific rotation
Ac	acetyl
acac	acetylacetonate
Ac_2O	acetic anhydride
aq.	aqueous
Ar	aromatic
Ar-C	aromatic carbon
Ar-H	aromatic proton
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bz	benzyl
Bu	butyl
C	quaternary carbon
c	cyclo
Cat	catalytic
Cbz	benzyloxycarbonyl
$CDCl_3$	deuterochloroform
CD_3OD	deuterated methanol
CH	carbon of CH (^{13}C NMR)
CH_2	carbon of CH_2 (^{13}C NMR)
CH_2Ph	CH_2 of Bn

CI +	chemical ionization (positive ion mode)
CN	cyano
CO	carbonyl carbon (^{13}C NMR)
conc.	concentration
COSY	correlation spectroscopy
CSA	camphorsulfonic acid
Cy	cyclohexyl
DBU	*N*,*N*′-dibutylurea
DCM	dichloromethane
d	doublet
dd	doublet of doublets (^{1}H NMR)
ddd	doublet of doublet of doublets (^{1}H NMR)
dddd	doublet of doublet of doublet of doublets (^{1}H NMR)
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
ddt	doublet of doublet of triplets (^{1}H NMR)
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhanced proton spin transfer
DH	dihydroxylation
$(DHDQ)_2$-AQN	dihydroquinidine-anthraquinone
$(DHQ)_2$-PHAL	hydroquinine 1,4-phthalazinediyl diether
$(DHQD)_2$-PHAL	hydroquinidine 1,4-phthalazinediyl diether
DIAD	diisopropyl azodicarboxylate
DIBALH	diisobutylaluminum hydride

DI-MS	direct insertion-mass spectrometry
DMAP	*N*,*N*-dimethyl-4-aminopyridine
DMDP	2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
D_2O	deuterium oxide
d.r.	diastereomeric ratio
dq	doublet of quartets (^{1}H NMR)
δ	chemical shift
EAE	experimental autoimmune encephalomyelitis
EDTA	ethylenediaminetetraacetic acid
ee	enantiomeric excess
EI	electron impact
ES -	electrospray ionization (negative ion mode)
ES +	electrospray ionization (positive ion mode)
Et	ethyl
et al.	and others
exp.	Experimental
eq. or equiv.	equivalent
FID	flame ionization detector
g	gram
GC-FID	gas chromatography-flame ionization detector
GC-MS	gas chromatography-mass spectrometry

gHSQC	gradient heteronuclear single quantum correlation
Grubb'II catalyst	benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium
H	proton (^{1}H NMR) or hydrogen
H^-	hydride ion
h	hour
HIV	human immunodeficiency virus
Hz	hertz
i-	iso-
IC_{50}	inhibitor concentration at 50% inhibition of enzyme
J	coupling constant (NMR)
KHMDS	potassium hexamethyldisilazane
kg	kilogram
K_i	inhibition constant
LDA	Lithium diisopropylamide
lit.	literature
M	molarity
m	multiplet
Me	methyl
Mes	mesityl or 2,4,6-trimethylphenyl
m-CPBA	*meta*-chloroperoxybenzoic acid

mg	milligram
MIC	minimum inhibition concentration
MOM	methoxymethyl
mp	melting point
Ms	mesyl or methanesulfonyl
MS	mass spectrometry
MW or MWt	molecular weight
m/z	mass-to-charge ratio
n-	normal-
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear Magnetic Resonance
NOESY	Nuclear Overhauser Effect Spectroscopy
PAHs	polycyclic aromatic hydrocarbons
PCBs	polychlorinated biphenyls
Pf	*N*-9-phenylfluoren-9-yl
Ph	phenyl
PMB	*para*-methoxybenzyl
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
Pr	propyl
psi	pound per square inch
PTLC	preparative thin layer chromatography
pyr	pyridine
quant.	quantitative

RA	retention area
RCM	ring-closing metathesis
RI	retention indices
rt	room temperature
s	singlet
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*tert*-butyldimethysilyl
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethysilyl
t	triplet
t	tert
THF	tetrahydrofuran
Tf	trifyl or trifluoromethanesulfonyl
TFAA	trifluoroacetic anhydride
TFA	trifluoroacetic acid
TIC	total-ion current
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propylammonium perruthenate
Tr	trityl
Ts	tosyl or toluenesulfonyl
Δ	heat

PART I

ISOLATION OF SOME BIOACTIVE COMPOUNDS FROM *HELIOTROPIUM INDICUM* LINN.