CHAPTER 1

INTRODUCTION

1.1 General Introduction

Zingiberaceae family comprises of approximately 47 genera and about 1500 species. Plants in this family are monocotyledon and grow naturally in tropical and sub-tropical forest in Asia, India and Australia [1].

Members of the Zingiberaceae family have been considered important as natural spices or as medicinal plants. The well-known examples of species used as spices are the rhizomes of *Zingiber officinale* (true ginger), *Curcuma domestica* (turmeric) and *Phaeomeria sp*. (kantan). Many other species have been used in traditional medicine including *Kaempferia galanga* (cekur), *Z. zerumbet* (lempoyang), *Alpinia galanga* (lengkuas) and *C. xanthorrhiza* (temu lawak).

1.2 *Curcuma xanthorrhiza*

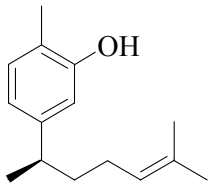
Curcuma xanthorrhiza, locally known as *temu lawak* or *shu gu jiang huang* (束骨薑黃) in Chinese is a zingiberaceous plant used medicinally in Southeast Asia. In Indonesia, its rhizome is widely used as a tonic and cholagogue. In Europe, it is employed in choleretic drug preparations. In Thailand, the rhizome of this plant is used by local people, especially in the eastern and northeastern parts of the country,

for the treatment of inflammation in postpartum uterine bleeding and also as an emmenagogue [2].

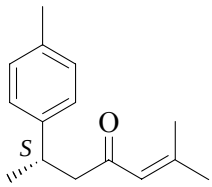
1.3 Chemical Constituents of *Curcuma xanthorrhiza*

Chemical constituents of *C. xanthorrhiza* have been well-investigated and previous studies on this species have yielded an assortment of monoterpenoids, sesquiterpenoids and diarylheptanoids.

The major constituent of *C. xanthorrhiza* is xanthorrhizol (1), a bisabolane-type sesquiterpenoid which was first isolated from rhizomes of *C. xanthorrhiza* in 1970 [3]. Xanthorrhizol (1) was also isolated from the root of Mexican medicinal plant, *Iostephane heterophylla* [4,5]. John et al. assigned the absolute configuration of (–)-xanthorrhizol (1) as *R*-configuration by the synthesis of (*S*)-(+)-xanthorrhizol from (*S*)-(+)-ar-turmerone (2) [6].



(1)

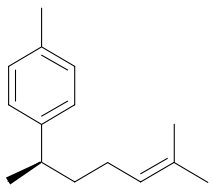


(2)

Previous investigations showed that xanthorrhizol (1) possessed various bioactivities. Aguilar et al. reported that (1) possessed antifungal activity against *Candida albicans*, toxicity against *Artemia salina* and cytotoxicity against human nasopharyngeal carcinoma cell line [5]. This sesquiterpenoid has been shown to inhibit contractions in rat uterus [7], and induced endothelium-independent relaxation of rat thoracic aorta [8]. Itokawa et al. reported that xanthorrhizol (1) showed antitumour properties [9]. Xanthorrhizol (1) was also found to show an antibacterial activity against *Streptococcus mutans* [10]. Further investigation on antibacterial activity of xanthorrhizol showed that this compound exhibited the highest antibacterial activity against *Streptococcus sp*. causing dental caries. These

results suggest that xanthorrhizol (1) can be formulated for food and dental products for preventing oral diseases [11].

Four bisabolane sesquiterpenes, ar-curcumene (3), ar-turmerone (4), β-atlantone (5) and xanthorrhizol (1) were isolated as antitumour constituents from the methanolic extract of the rhizomes of *C. xanthorrhiza* [9].



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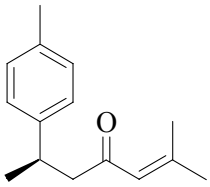

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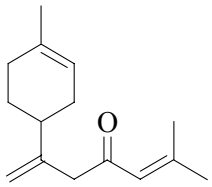
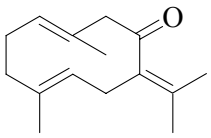


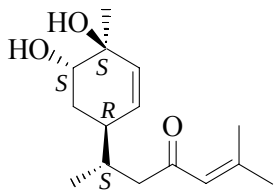
(5)

A low melting point colourless needles compound has been isolated from the methanol extract of *C. xanthorrhiza*, which was identified as germacrone (6). This compound showed hypothermic effect to mice [12] and anti-inflammatory action [13].



(6)

Uehara et al. isolated three new bisabolane sesquiterpenenoids, namely bisacurone (7), bisacumol (8), and bisacurol (9) from chloroform-soluble fractions of the rhizomes of *C. xanthorrhiza*. Besides that, one known compound, curlone (10) was also isolated in this investigation. Spectroscopy, chemical conversion and CD exciton chirality have been employed in determining the absolute structures of these new compounds [14].



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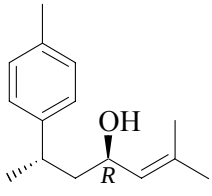

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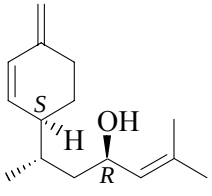

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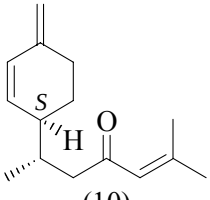
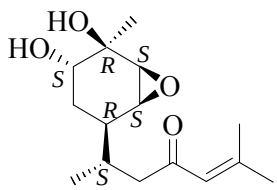


(10)

Further investigation of the chloroform-soluble fractions of the rhizomes of *C. xanthorrhiza* by the same group afforded four new bisacurone related compounds, namely bisacurone epoxide (11), bisacurone A (12), bisacurone B (13) and

bisacurone C (14). Compound (11) was converted to its monoacetate to determine its relative stereostructure by X-ray crystallography [15].



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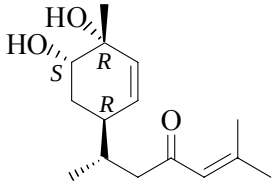

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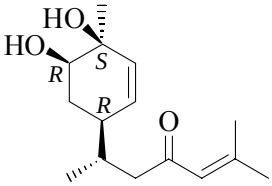

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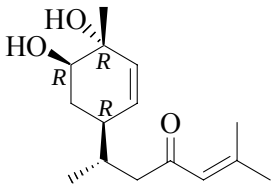
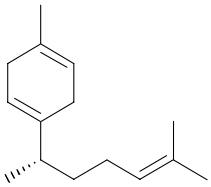


(14)

In the course of investigating terpenoids and curcuminoids in the fresh rhizomes of *C. xanthorrhiza*, Uehara et al. isolated nine sesquiterpenoids, xanthorrhizol (1), ar-curcumene (3), ar-turmerone (4), germacrone (6), β-curcumene (15), β-sesquiphellandrene (16), curzerenone (17) and α-turmerone (18) [16].



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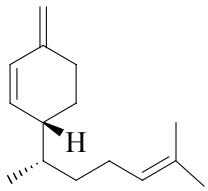

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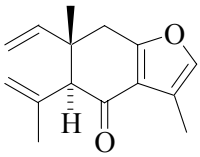

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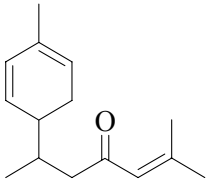
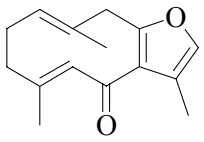


(18)

In 1993, Pandji and co-workers investigated the insecticidal constituents from four species of Zingiberaceae, including *C. xanthorrhiza*. In this study, furanodienone (19) was isolated from the rhizomes [17]. Another closely related sesquiterpenoids, furanodiene (20) was isolated from the rhizomes of Malaysian *C. xanthorrhiza* [18].



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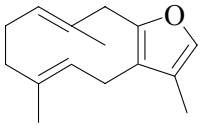
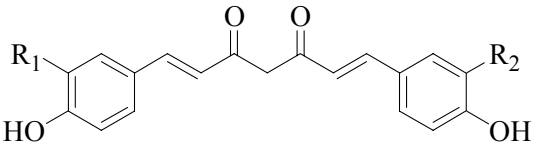


(20)

Besides sesquiterpenoids, diarylheptanoids have also been found abundant in the rhizomes of *C. xanthorrhiza*. Three major diarylheptanoids, curcumin (21), demethoxycurcumin (22) and bisdemethoxycurcumin (23) have been isolated from the rhizomes of this species [19].



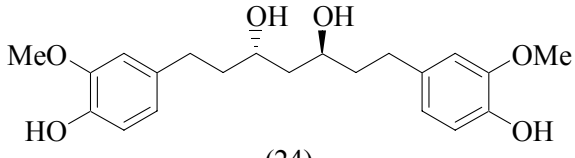
(21) : $R_1 = OCH_3$, $R_2 = OCH_3$
(22) : $R_1 = OCH_3$, $R_2 = H$
(23) : $R_1 = H$, $R_2 = H$

These three curcuminoids was also isolated from turmeric (*Curcuma longa* Linn.). The yellow pigment of *C. xanthorrhiza* and other *Curcuma sp.*, curcumin was isolated as early as 1815 [20] and in 1870, Daube isolated it in crystalline form [21]. The structure of curcumin was elucidated in 1910 by Lampe and co-workers [22] and synthesised by the same group in 1918 [23]. Roughley studied the biosynthesis of curcumin and completed the synthesis of curcumin in 1973 [24].

Curcumin shows a variety of pharmacological effects. Among others, curcumin is an antioxidant agent, showed radical-scavenging antioxidant activity against lipid peroxidation in various media, and suppressed free-radical-induced oxidation of methyl linoleate in solutions and aqueous emulsion. Curcumin is comparable to isoeugenol as an antioxidant [25].

Curcumin has also been reported to possess anti-inflammatory properties [26, 27] and inhibits platelet aggregation [28]. Curcumins (21-23) have been shown to possess antiprotozoal activities against *Plasmodium falciparum* and *Leishmania major* [29]. Recently, Eun-kyoung Song et al. reported that compounds (21-23) showed free radical scavenging effects and showed significant hepatoprotective effects on tacrine-induced cytotoxicity in human liver-derived Hep G2 Cells [30].

Uehara et al. have isolated two new diarylheptanoids, octahydrocurcumin [(3*S*,5*S*)-1,7-bis(4-hydroxy-3-methoxyphenyl)-heptane-3,5-diol] (24) and 1-hydroxy-1,7-bis(4-hydroxy-3-methoxyphenyl)-6-heptene-3,5-one (25) and two known diarylheptanoids dihydrocurcumin (26) and hexahydrocurcumin (27) from methanol extract of *C. xanthorrhiza* [31].



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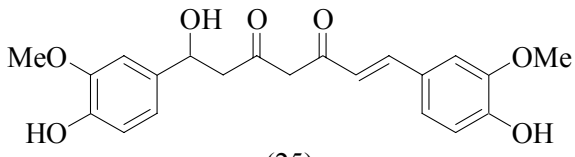

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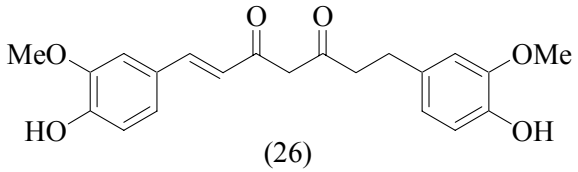

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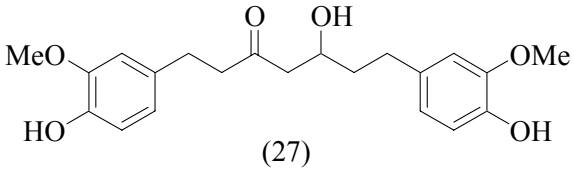
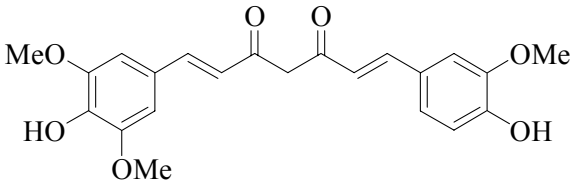


(27)

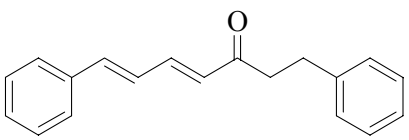
Masuda et al. isolated another curcuminoid from the acetone extract of *C. xanthorrhiza* rhizomes. Its structure has been assigned as 1-(4-hydroxy-3,5-dimethoxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-(1*E*,6*E*)-1,6-heptadiene-3,4-dione (28) based on its spectral data.



(28)

Compound (28) showed potent antioxidant activity against autooxidation of linoleic acid in a water-alcohol system and it showed slightly stronger antioxidant efficiency than curcumin (21) [19].

Bioassay-guided fractionation of hexane extract of this species has yielded three non-phenolic diarylheptanoids, identified as *trans*,*trans*-1,7-diphenyl-1,3-heptadien-5-one (alnustone) (29), *trans*-1,7-diphenyl-1-hepten-5-ol (30) and *trans*,*trans*-1,7-diphenyl-1,3-heptadien-5-ol (31). Compound (31) was reported for the first time as a plant constituent. Besides that, cinnamaldehyde (32) has also been isolated and identified. All the three non-phenolic diarylheptanoids showed significant anti-inflammatory activity in the assay of carragenin-induced hind paw edema in rats [32].



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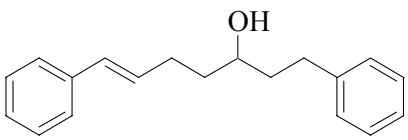

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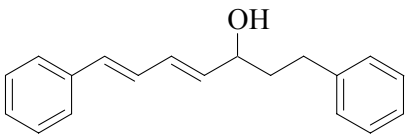

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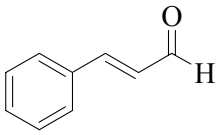
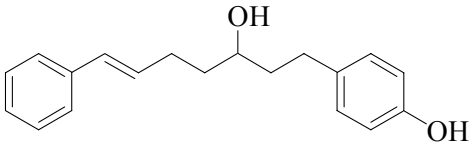


(32)

Suksamaran et al. isolated two new phenolic diarylheptanoids from the ethanolic extract of *C. xanthorrhiza* cultivated in Thailand. These two compounds have been identified as 5-hydroxy-7-(4-hydroxyphenyl)-1-phenyl-(1*E*)-1-heptene (33) and 7-(3,4-dihydroxyphenyl)-5-hydroxy-1-phenyl-(1*E*)-1-heptene (34) [2].



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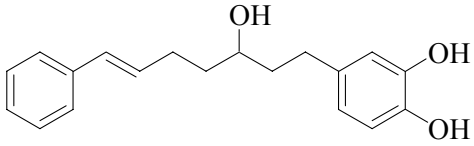
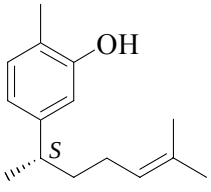


(34)

1.4 Syntheses of Xanthorrhizol (1)

Xanthorrhizol (1) has been found to show many useful bioactivities and as a result, intense synthetic efforts have been directed towards the synthesis of xanthorrhizol (1) since the first isolation of this compound by Rimpler et al. from rhizomes of *C. xanthorrhiza* Roxb. [3]. To the best of our knowledge, nine syntheses have been reported for the syntheses of xanthorrhizol (1). Four syntheses of the racemate [33-37], three syntheses of *S*-(+)-xanthorrhizol (35) [6, 38-39] and two syntheses of *R*-(–)-xanthorrhizol (1) [40-41] have been reported. The syntheses leading to nonracemic material is the conversion of (+)-ar-turmerone (4) into *S*-(+)-xanthorrhizol (35) [6] and the conversion of (–)-parvifoline (36) into (–)-xanthorrhizol (1). Meyers [38] and Fuganti [39] completed the asymmetric total synthesis of *S*-(+)-(35). In 1999, enantiocontrolled total synthesis of *R*-(–)-xanthorrhizol (1) has been completed by Sato et al. [41].



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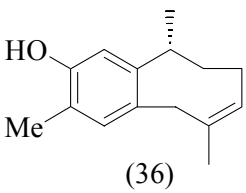
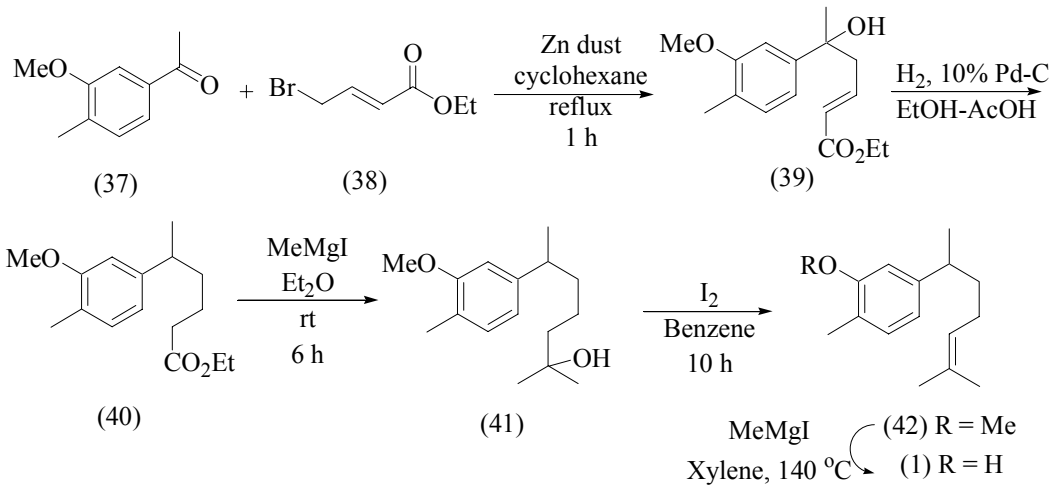


(36)

1.4.1 Rane's Short Synthesis of Xanthorrhizol (1) [35]

The Rane's synthesis of xanthorrhizol (1) started with Reformatsky reaction of 3-methoxy-4-methylacetophenone (37) with ethyl 4-bromocrotonate (38) to give ethyl 5-hydroxy-(3-methoxy-4-methylphenyl)-2-hexenoate (39) followed by hydrogenation over Pd-C in the presence of acetic acid to form ethyl 5-(3-methoxy-4-methylphenyl)hexanoate (40) in high yield. Grignard reaction and iodine dehydration furnished xanthorrhizol methyl ether (42) as shown in **Scheme 1.1**. A short synthesis (four-steps) of xanthorrhizol methyl ether (42) has been achieved compared to the ten-step earlier synthesis [33].

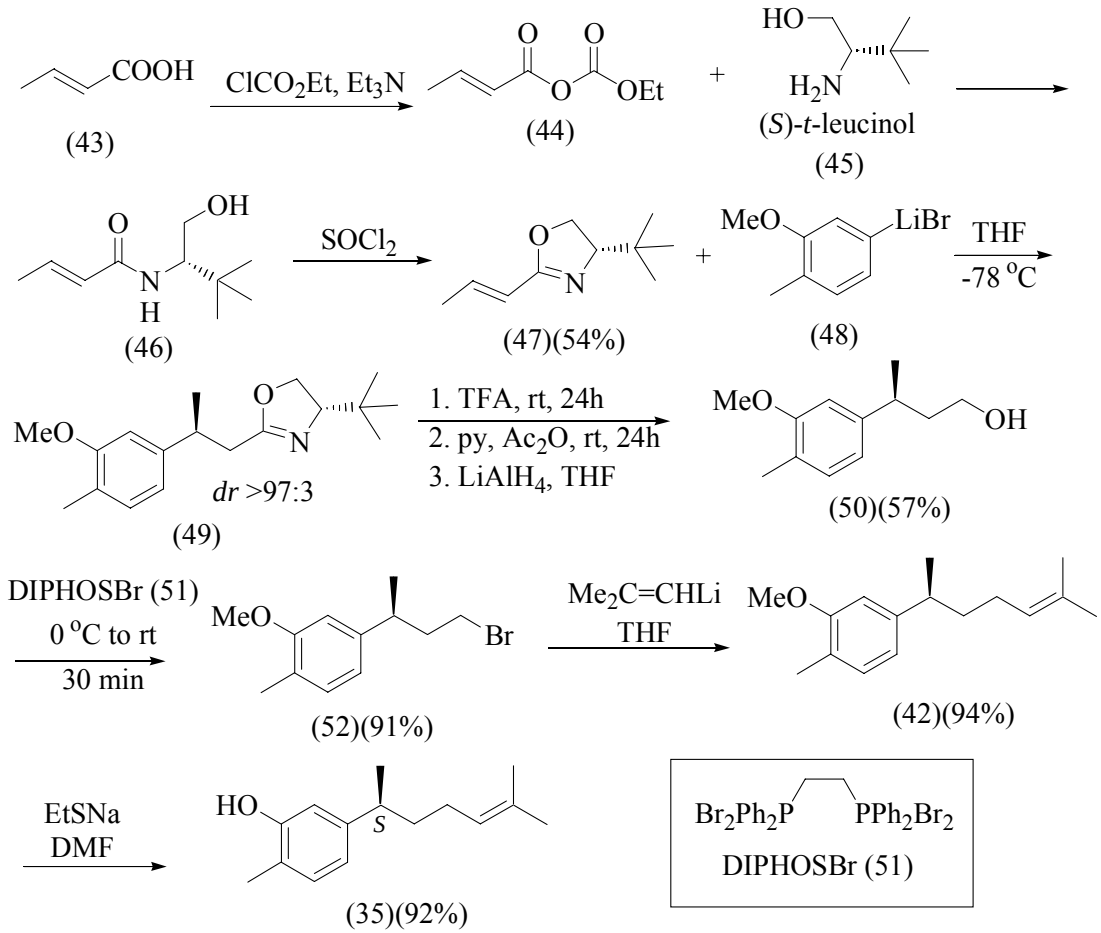


Scheme 1.1: Rane's synthesis of xanthorrhizol (1).

1.4.2 Meyers' Asymmetric Synthesis of *S*-(+)-Xanthorrhizol (35) [38]

In 1997, Meyers and Stoianova reported the asymmetric synthesis of *S*-(+)-xanthorrhizol (35) which is summarised in **Scheme 1.2**. The key chiral oxazoline (47) was prepared in three steps from crotonic acid (43). First, crotonic acid (43) was treated with $ClCO_2Et$ to furnish the mixed anhydride (44), then the resulting mixed anhydride (44) was reacted with *t*-leucinol (45) to form amide (46). Cyclisation of the resulting amide (46) with $SOCl_2$ gave oxazoline (47) in 54% yield. Stereoselective addition of (*o*-methoxy-*p*-tolyl)lithium (48) to the chiral α,β-

unsaturated oxazolines (47) gave compound (49). Analysis of the chromatographed addition products (49) revealed that the diastereomeric ratio was at least 97:3. Alcohol (50) was obtained by acid hydrolysis, acetylation and reduction of oxazoline derivative (49). Alcohol (50) was then treated with 1,2-bis(diphenylphosphino)-ethane tetrabromide (DIPHOSBr) (51) to yield the bromide (52). Treatment of bromide (52) with (2,2-dimethylvinyl)lithium gave xanthorrhizol methyl ether (42) in high yield (94%) and cleavage of the methyl ether (42) using sodium ethanethiolate in DMF gave *S*-(+)-xanthorrhizol (35).

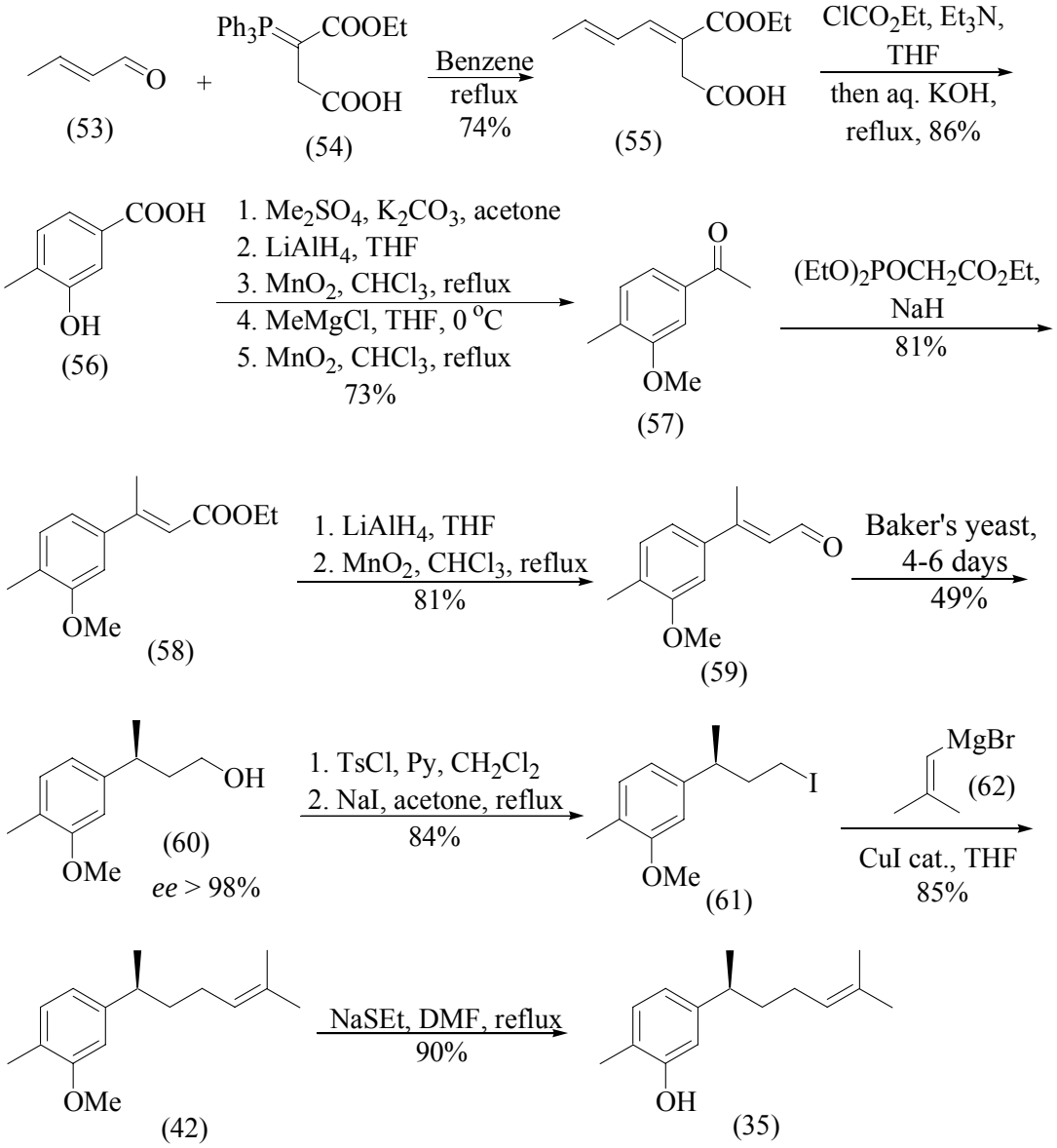


Scheme 1.2: Meyers' asymmetric synthesis of *S*-(+)-xanthorrhizol (35).

1.4.3 Fuganti's Baker's Yeast-mediated Enantioselective Synthesis of *S*-(+)-Xanthorrhizol (35) [39]

The most recent total synthesis of xanthorrhizol (1) came from the Fuganti's group as shown in **Scheme 1.3** [39]. In their synthesis, the aromatic ring (56) was constructed by benzanullation of the hexadienoic acid derivative (55). Compound (55) was submitted to cyclisation using ethyl chlorochromate and triethylamine as base, followed by treatment with KOH to give the acid (56), which was then converted to benzophenone (57) in good yield by a number of straightforward synthetic steps. The ester (58) was synthesised from the substituted acetophenone (57) by Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate (ethyl diethoxyphosphosphorylacetate) and sodium hydride.

The key step in this synthesis was Baker's yeast-mediated enantioselective conversion of the unsaturated aldehyde (59) into the saturated alcohol (60). The result of the reduction showed a high conversion of the aldehyde (59) into the saturated *S*-(+)-alcohol (60) (49% isolated yield) and gave good enantioselectivity with enantiomeric excess >98%. To this end, the enantiopure alcohol (60) was converted into the iodide (61) *via* the tosyl ester derivatives and substitution with sodium iodide in acetone. The coupling of the iodide (61) with the Grignard reagent (62) catalysed by copper(I) iodide furnished enantiopure (42). Demethylation of compound (42) using sodium ethanethiolate in DMF afforded (*S*)-(+)-xanthorrhizol (35)



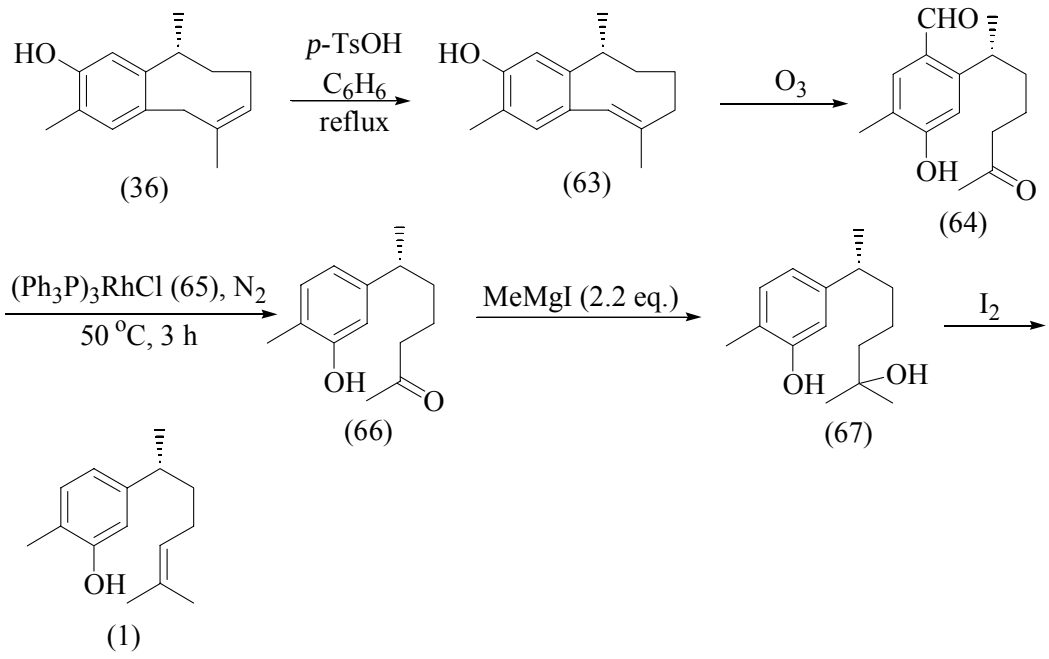
Scheme 1.3: Fuganti's Baker's yeast-mediated enantiosynthesis of *S*-(+)-xanthorrhizol (35).

1.4.4 Conversion of Parvifoline (36) to *R*-(–)-Xanthorrhizol (1) [40]

Parvifoline (36) is a benzocyclooctene originally isolated from *Cereopsis parvifolia* [42]. It was also found in *Pereziae alamani* var. *oolepsis* [43], *P. carpholepis* [44] and *P. longifolia* [45].

Garcia and co-workers have converted parvifoline (36) to xanthorrhizol (1) in five steps, as shown in **Scheme 1.4**. The first step was acid catalysed isomerisation of

parvifoline (36) to isoparvifoline (63). Ozonolysis of isoparvifoline (63) produced aldehyde (64). Aldehyde (64) was decarbonylated with Wilkinson's reagent (chloro-*tris*-(triphenylphosphine)rhodium) (65) to give 5-(2'-ketoheptan-6'-yl)-2-methylphenol (66). Reactions of this intermediate with CH_3MgI followed by dehydration yielded *R*-(–)-xanthorrhizol (1). This was the first synthesis of xanthorrhizol (1) with *R*-configuration.



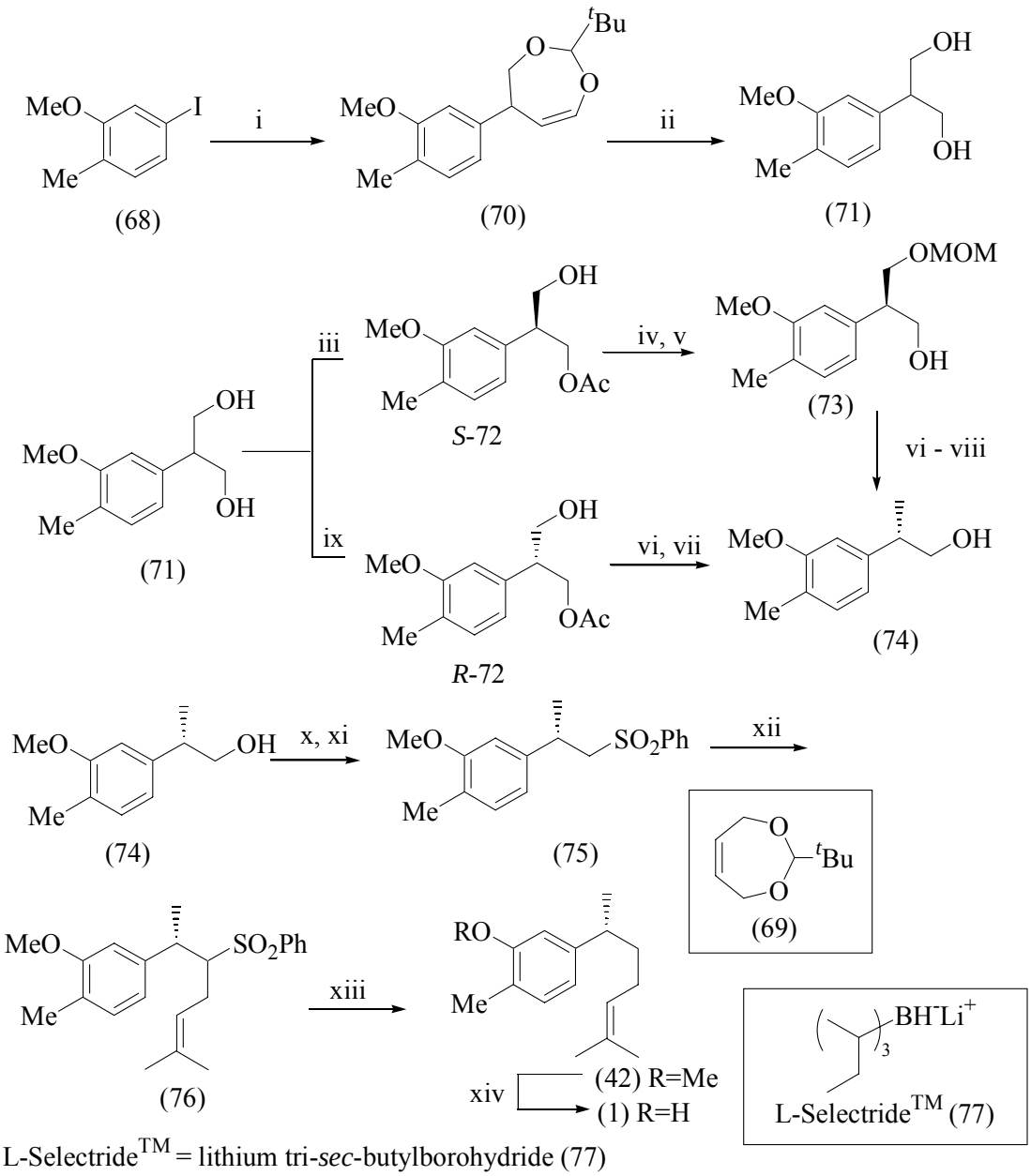
Scheme 1.4: Conversion of parvifoline (36) to *R*-(–)-xanthorrhizol (1).

1.4.5 Shishido's Enantiocontrolled Total Synthesis of *R*-(–)-Xanthorrhizol (1)

The Shishido group has published an efficient and enantiocontrolled total synthesis of *R*-(–)-xanthorrhizol (1) [41]. This synthesis started with Heck reaction between 4-iodo-2-methoxytoluene (68) and 2-*tert*-butyl-4,7-dihydro-1,3-dioxepine (69) to form coupled product (70). Product (70) was submitted to ozonolysis followed by reductive workup with sodium borohydride ($NaBH_4$) to give the σ-symmetrical prochiral 2-aryl-1,3-propanediol (71). Prochiral diol (71) was subjected to asymmetric acetylation utilizing *Candida antacrtica* lipase (CAL) with vinyl

acetate as an acyl donor to afford an optically active monoacetate *S*-(72) with 94% *ee*. On the other hand, PPL-catalysed acetylation of (71) in ether yielded the desired monoacetate *R*-(72) with 83% *ee* in 95% yield. The *R*-monoacetate was then tosylated and reductively deoxygenated with $NaBH_4$ in hot DMSO to produce the *S*-alcohol (74) in 65% yield in two steps. The monoacetate *S*-(72) was successfully converted to *S*-(74) *via* a five-step sequence of reactions. Methoxymethylation of *S*-(72) followed by alkaline hydrolysis gave (73). Compound (73) was submitted to tosylation, reductive deoxygenation and acidic hydrolysis to provide *S*-alcohol (74). Then, *S*-alcohol (74) was transformed into sulphone (75) in two steps reaction. Prenylation of (75) was accomplished by treatment of (75) with *n*-butyllithium followed by prenyl bromide to afford phenylsulphonate (76). Reductive removal of the benzenesulphonyl group in (76) was achieved by treating with 5% sodium amalgam in buffered methanol to give *O*-methylxanthorrhizol (42). L-Selectride® (Lithium tri-*sec*-butylborohydride) (77) was used in this final step of the synthesis to cleave the methyl functionality of compound (42) to produce *R*-(–)-xanthorrhizol (1), the naturally occurring xanthorrhizol.

The strength of this synthesis lies in the utilisation of lipase-mediated chemoenzymatic transformation to construct benzylic tertiary stereogenic centre. The convergent strategy to obtain *R*-alcohol (74) is also noteworthy. **Scheme 1.5** summarised the sequence of the synthetic methodology.



L-Selectride™ = lithium tri-*sec*-butylborohydride (77)

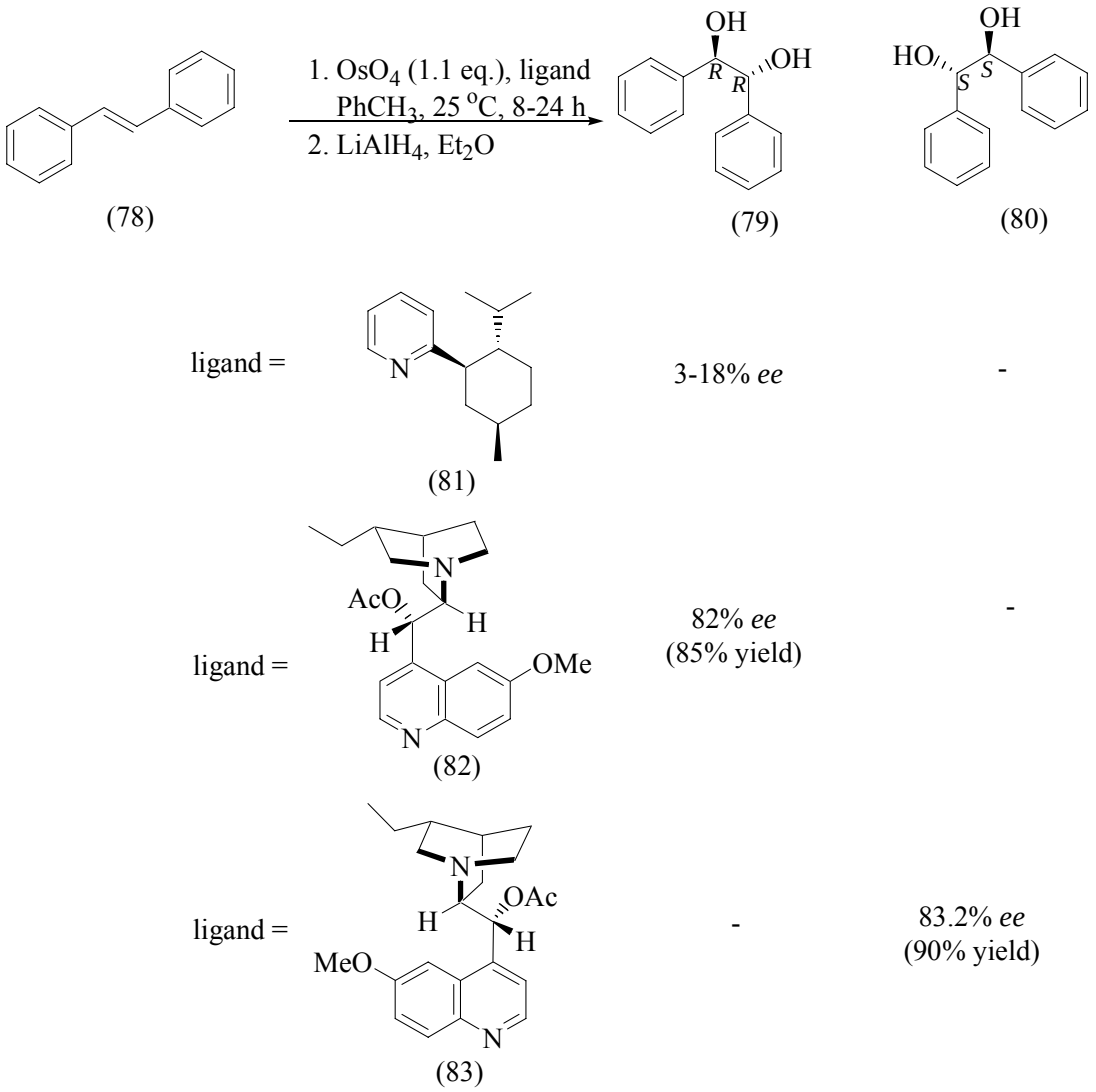
Scheme 1.5: Shishido's enantiocontrolled total synthesis of (–)-xanthorrhizol (1).

Reagents & Conditions: (i) 2-*tert*-butyl-4,7-dihydro-1,3-dioxepine (69), $Pd(OAc)_2$, Ph_3P, *i*-Pr_2NEt, DMF, 80 °C, 75%; (ii) O_3, CH_2Cl_2, MeOH (1:1), -78 °C then $NaBH_4$, rt, 63%; (iii) CAL, vinyl acetate, Et_2O, rt, 19%; (iv) MOMCl, *i*-Pr_2NEt, 4-DMAP, CH_2Cl_2, rt, 81%; (v) $LiAlH_4$, THF, rt; (vi)TsCl, Et_3N, 4-DMAP, CH_2Cl_2, rt; (vii) $NaBH_4$, DMSO, 60 °C, 72% (3 steps) for the MOM ether (74), 65% (2 steps) for *R*-73; (viii) 10% HCl (aq.), MeOH, rt, 95%; (ix) PPL, vinyl acetate, Et_2O, 39 °C, 95%; (x) nBu_3P, prenyl bromide, HMPA, Ph_2S, pyridine, rt, 84%; (xi) MCPBA, $KHCO_3$, CH_2Cl_2, rt, 100%; (xii) *n*-BuLi, prenyl bromide, HMPA, THF, -78 °C, 82%; (xiii) Na-Hg, Na_2HPO_4, MeOH, rt, 83%; (xiv) L-Selectride® (77), THF, reflux, 78%.

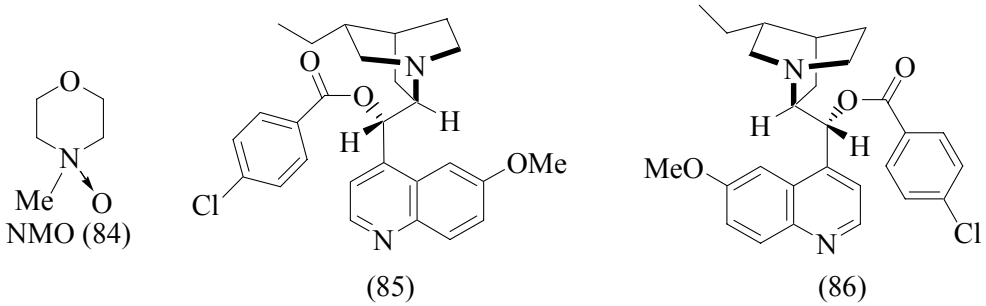
1.5 The Sharpless Asymmetric Dihydroxylation

The *cis* dihydroxylation of olefins mediated by osmium tetroxide represents an important general method for olefin functionalisation [46]. The original dihydroxylation used stoichiometric amounts of OsO_4, which is expensive, volatile, and toxic. Over the years, the original dihydroxylation procedure has been modified to operate the use of OsO_4 in catalytic amounts, more rapid and better yield, this has been achieved by Sharpless [47-50].

In Sharpless asymmetric dihydroxylation (AD), the source of asymmetric is a chiral amine, which forms a complex with OsO_4. In 1980, Sharpless used pyridine (81), derived from menthol, induced *ee*'s of 3-18% in the dihydroxylation of *trans*-stilbene (78), as shown in **Scheme 1.6**. Nevertheless, the reaction had to be improved because the *ee*'s were too low. In the same paper, Sharpless disclosed that dihydroxylation of olefins in the presence of dihydroquinidine acetate (82) or dihydroquinine acetate (83) under stoichiometric conditions gave optically active diols with 25-94% *ee* after hydrolysis. Cost considerations make this stoichiometric osmylation uneconomical [51]. Breakthrough was made in 1987 when Sharpless and co-workers discovered that the stoichiometric process become catalytic when *N*-methylmorpholine-*N*-oxide (NMO) (84) was used as the co-oxidant in the dihydroxylation. In this landmark paper, dihydroquinidine *p*-chlorobenzoate (85) and dihydroquinine-*p*-chlorobenzoate (86) also were introduced as new chiral ligands with improved enantioselective properties. The communication described the catalytic AD of *trans*-stilbene (78) with 0.2 mol% of OsO_4, 0.134 eq. of chiral auxiliary, and 1.2 eq. of NMO (84) as oxidant to give (*R*,*R*)-(+)-dihydrobenzoin (79) in 80% yield with 88% *ee* [52].

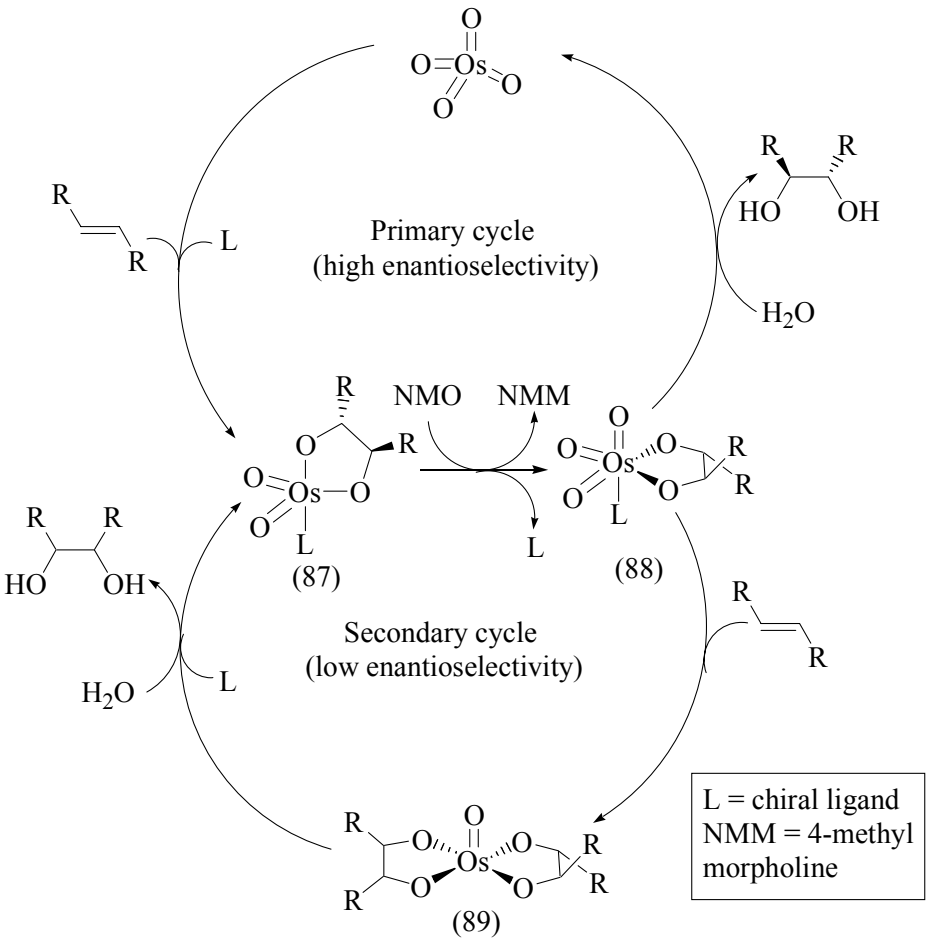


Scheme 1.6: The first enentioselective dihydroxylation reactions developed by Sharpless.



Since then, four substantial improvements were made to the AD: (a) change of the stoichiometric oxidant from NMO to $K_3Fe(CN)_6$-K_2CO_3, (b) method for effecting increase in the rate of reaction, (c) new class of "dimeric" ligand combining two alkaloid units linked by an aromatic "spacer" unit, (d) a more convenient source of osmium(VIII).

The catalytic cycle for the Sharpless AD with NMO (84) as a co-oxidant is shown in **Scheme 1.7**. The enantiomeric excess decreased when changing from stoichiometric to catalytic conditions. The reason for this phenomenon is due to a second catalytic cycle in which the chiral ligand is not involved [53]. The osmium(VIII) trioxoglycolate (88) has access to a secondary reaction cycle, forming a bisglycolate (89), hydrolysis of the glycolate give racemic diol [54]. However, when the catalytic system $K_3Fe(CN)_6$-K_2CO_3 in *t*-BuOH-H_2O is used [55], the oxidant is confined to the aqueous phase, allowing the osmium(VI) glycolate (87) to hydrolyse in the organic phase before being reoxidised.

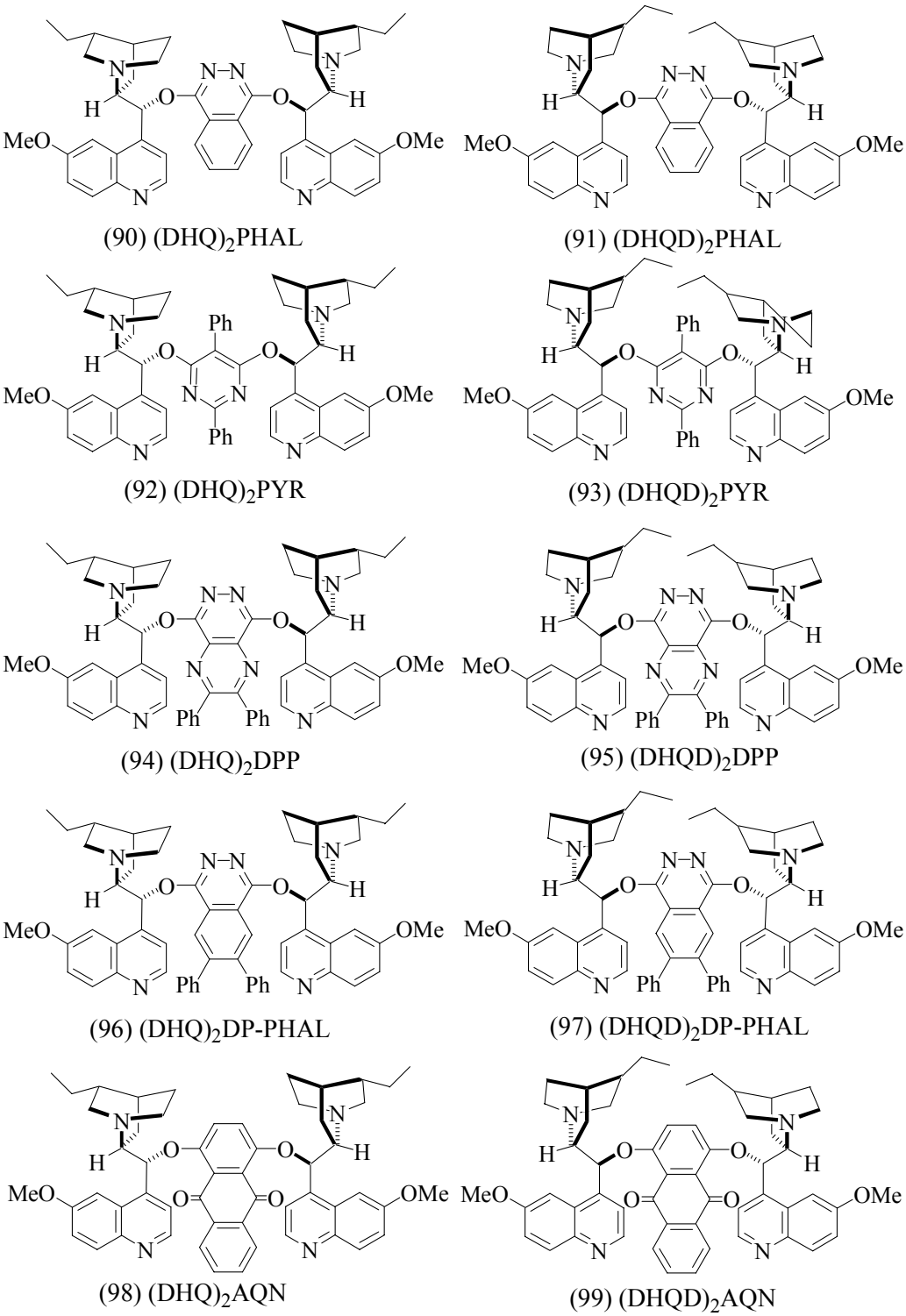


Scheme 1.7: The two catalytic cycles for the Sharpless AD with NMO as a co-oxidant.

Slow reaction of trisubstituted olefins is due to the slow hydrolysis of the osmium glycolate. However, this hydrolysis can be accelerated by addition of methane sulphonamide. The reaction time can be as much as 50 times shorter in the presence of this additive [56].

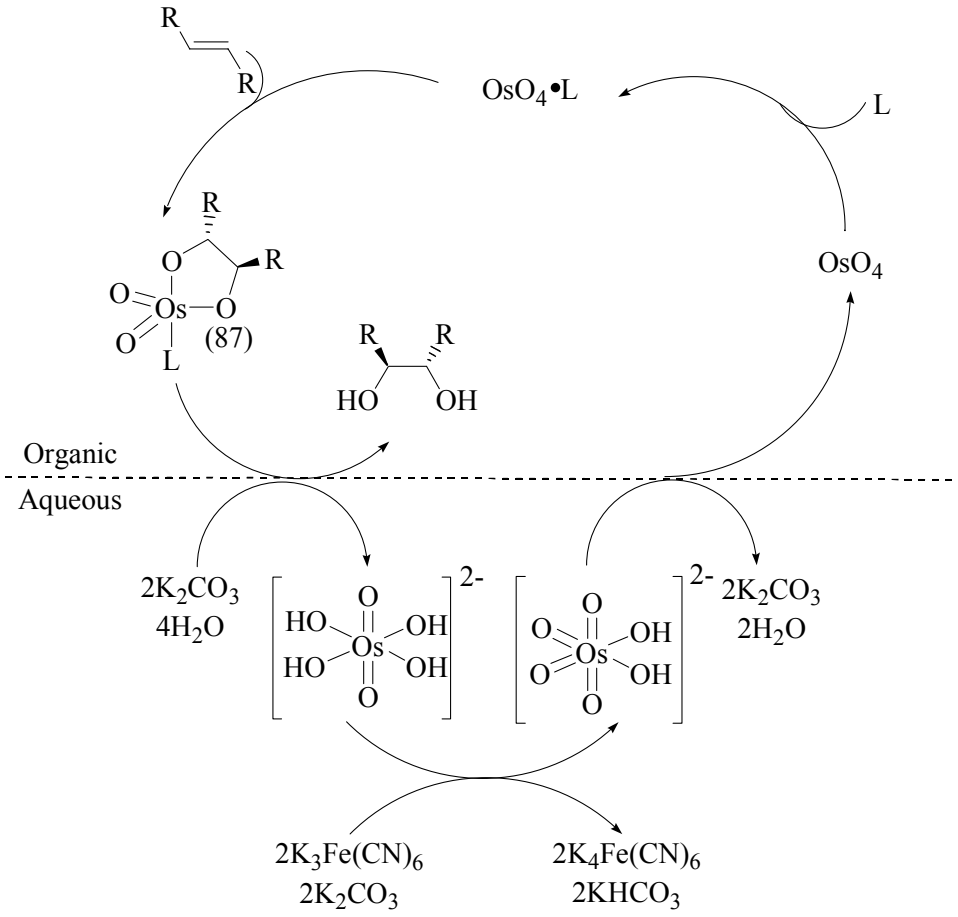
Until 1996, over 500 different ligands have been tested and a list of the most useful ligands can be subsequently be drawn (**Figure 1.1**). Among these the PHAL (phthalazine) ligands (90,91) are the most widely used in the AD due to their large substrate applicability and are currently employed in the AD-mix formulations [56]. The analogs of PHAL ligands, bis-cinchona alkaloid ligands with a diphenyl pyrazinopyridazine spacer (DPP) (94,95) and a diphenyl phthalazine spacer (DP-PHAL) (96,97) are also found to give excellent enantioselectivities in the AD of olefins. The enantioselectivies using these ligands are generally greater than or equivalent to those of ligands (90,91) [57]. The diphenylpyrimidine (PYR) (92,93) class is usually suitable for sterically congested olefins (especially terminal olefins) [58]. In 1996, anthraquinone (AQN) ligands (98,99) were introduced. The anthraquinone-based ligands lead to excellent results in the AD reactions of allylically substituted terminal olefins. These ligands give superior enantioselectivity in the AD of almost all olefins having only aliphatic substituents [59].

Finally, osmium tetroxide has been replaced by non-volatile osmium source, potassium osmate(VI) dihydrate [$K_2OsO_2(OH)_4$]. Until this point, all of the ingredients in the AD are solids and an AD-mix formulation of the standard reactants has been developed. These "AD-mixes" can be readily prepared, and there are also commercially available as AD-mix-α [$(DHQ)_2PHAL$] and AD-mix-β [$(DHQD)_2PHAL$]. The contents in 1kg of AD-mix are as follows: $K_3Fe(CN)_6$, 699.6g; K_2CO_3, 293.9g; $(DHQD)_2$- or $(DHQ)_2$-PHAL, 5.52g; and $K_2OsO_2(OH)_4$, 1.04g (**Figure 1.1**). AD procedure needs 1.4g of this AD-mix per millimole of olefin. The solvent used for the reaction is a 1:1 mixture of *t*-BuOH and water. The solvent mixture separates into two liquid phases upon addition of the inorganic reagents. The catalytic cycle for AD under this condition is shown in **Scheme 1.8**.



reagents	$(DHQ)_2PHAL$	$(DHQD)_2PHAL$	$K_2OsO_2(OH)_4$	$K_3Fe(CN)_6$	K_2CO_3
AD-mix-α	5.52 g	–	1.04 g	699.6 g	293.9 g
AD-mix-β	–	5.52 g	1.04 g	699.6 g	293.9 g

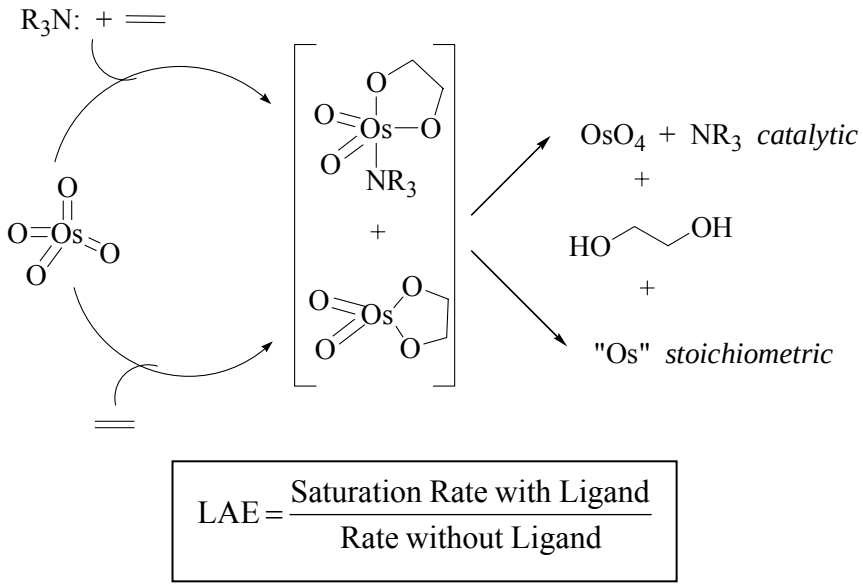
Figure 1.1: Structure of phthalazine (90,91), pyrimidine (92,93), diphenylpyrazinopyridazine (DPP) (94,95), diphenylphthalazine (DP-PHAL) (96,97) and anthraquinone (AQN) (98,99) ligands used in the Sharpless AD and composition of AD-mix-α and AD-mix-β.



Scheme 1.8: Catalytic cycle for asymmetric dihydroxylation using potassium ferricyanide as co-oxidant.

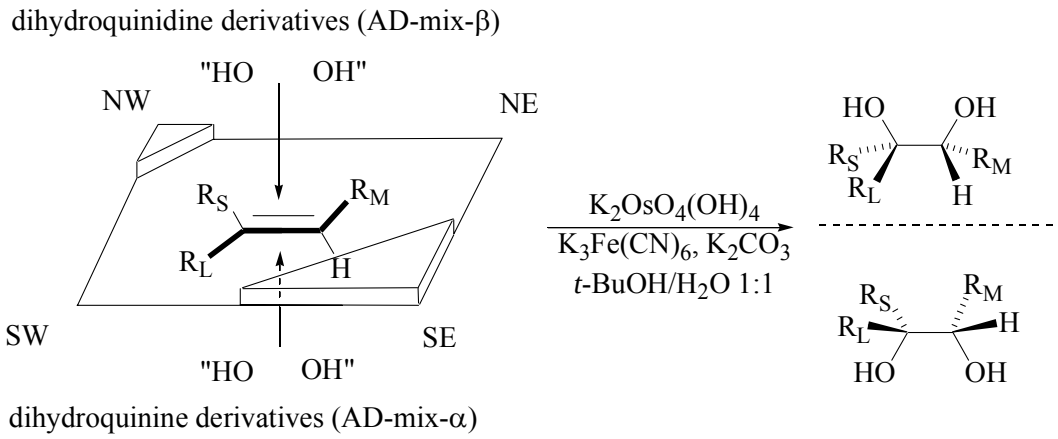
First, osmylation of the olefin proceeds to form the osmium(VI) glycolate-amine complex (87). Formation of (87) is presumed to occur in the organic phase in which all the involved species are soluble. Next, at the organic-aqueous interface, hydrolysis of the glycolate ester releases the diol into the organic phase and the reduced osmium as the hydrated osmate(VI) dianion into the aqueous phase. Oxidation of osmate(VI) by potassium ferricyanide regenerates osmium tetroxide *via* an intermediate perosmate(VIII) ion gives osmium tetroxide, which then migrates back into the organic phase to restart the cycle.

Sharpless AD is a type of ligand-accelerated catalysis because the addition of bis-cinchona ligand increases the reaction rate of this catalytic transformation. The principle of ligand acceleration is illustrated in **Scheme 1.9** for the AD reaction [60].



Scheme 1.9: The osmylation of olefins.

Scheme 1.10 presents a mnemonic showing olefin orientation and face selectivity. In the mnemonic, the olefin is oriented to fit the size constraints, where R_L = largest substituent, R_M = medium-sized substituent, and R_S = smallest substituent other than hydrogen. The oxygens will then be delivered from the upper face if dihydroquinidine (DHQD) derived chiral auxiliary is used and from the lower face if a dihydroquinine (DHQ) derived auxiliary is used.

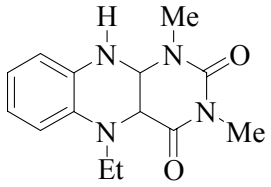


Scheme 1.10: Mnemonic device for the AD of olefins.

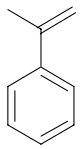
1.5.1 Recent Developments in Asymmetric Dihydroxylation

Mehltretter et al. demonstrated that the dihydroxylation in the presence of osmium tetroxide is largely pH dependent. It was found that the reaction rates for 1,2-di-, tri-, and tetrasubstituted olefins improved at a constant pH of 12.0. In addition, the enantioselectivity of terminal olefins at room temperature is slightly enhanced by using a constant pH of 10 [61].

The most widely used co-oxidant for the Sharpless AD is $K_3Fe(CN)_6$ and another widely used reoxidant is NMO (84). Besides that, reports on the utilisation of oxygen-based reoxidants such as air, O_2 and H_2O_2 have also been published. Bäckvall and co-workers developed a H_2O_2 reoxidation process for Os(VI) by using NMO (84) together with flavin (100) as co-catalysts in the presence of hydrogen peroxide [62]. Krief et al. successfully designed a reaction system consisting of oxygen, catalytic amount of OsO_4, $(DHQD)_2PHAL$ (91) and selenides for the dihydroxylation of α-methylstyrene (101) under irradiation with visible light [63].



(100)



(101)

Döbler et al. reported the osmium-catalysed dihydroxylation of aliphatic and aromatic olefins using molecular oxygen or air as the stoichiometric oxidant, but the enentioselectivities are occur lower than those of the classical $K_3Fe(CN)_6$ co-oxidant system [64]. Mehltretter and co-workers developed a procedure for the dihydroxylation of olefins using bleach (NaClO) as the terminal oxidant. Olefins give the optically active diols in the presence of chiral ligand with good to excellent chemo- and enantioselectivities under optimised pH conditions. This new protocol has distinct advantages. Compared to the dihydroxylation using hydrogen peroxide as oxidant, the procedure has the advantage that no co-catalyst (flavin, NMO) need to be added. Compared to the dihydroxylation using dioxygen this procedure is faster and easier to perform [65]. Sodium chlorite ($NaClO_2$) is the most recently reported reoxidant in Sharpless AD. Enantioselectivities of the $NaClO_2$ AD-process are

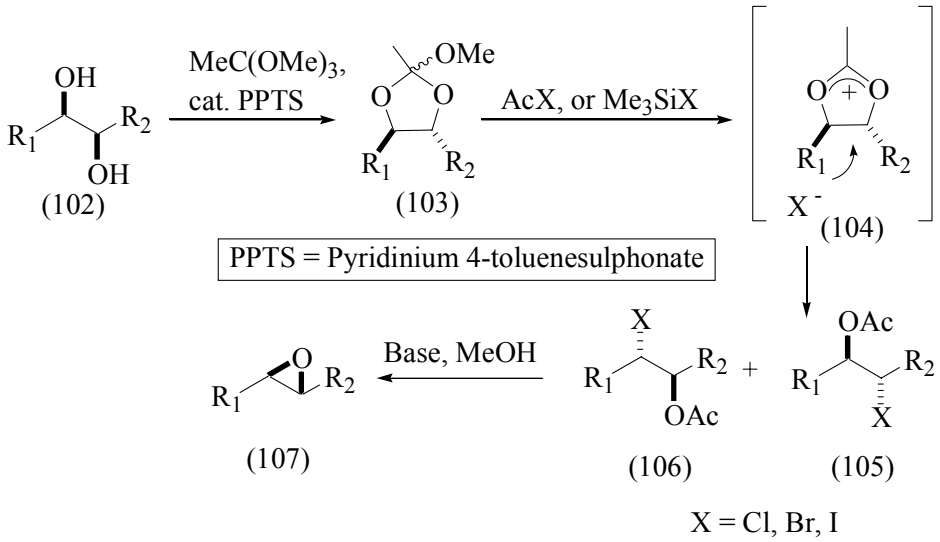
comparable with the enantioselectivities of other AD-processes and the yields are good [66].

1.5.2 Synthetic Application for 1,2-diols

If the *syn*-1,2-diol is not the final functionality required, manipulation of the starting chiral compound can be performed. The first convenient approach is the conversion of diols into acetoxy halides and conversion into epoxides. The second method is the regioselective conversion of one of the hydroxyl group into sulphonate ester.

1.5.2.1 Conversion of Diols into Halohydrin Esters and Epoxides

1,2-Diols (102) are converted in excellent yields to acetoxychlorides or acetoxybromides (105,106) *via* acetoxonium ion intermediate (104), as shown in **Scheme 1.11**.

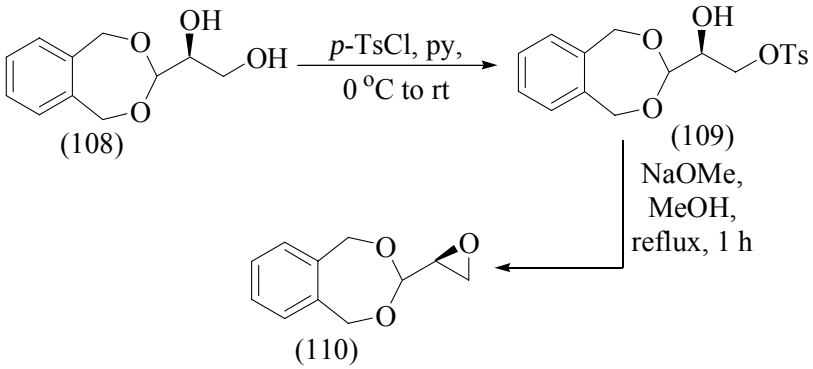


Scheme 1.11: Formation of acetoxy halides and epoxides *via* cyclic acetoxonium ions (104).

The cyclic orthoacetate (103) is prepared by acid-catalysed [pyridinium 4-toluenesulphonate (PPTS)] transesterification of diol (102) with a slight excess of trimethyl orthoacetate. The cyclic orthoacetate (103) is then treated with Me_3SiCl, acetyl chloride or acetyl bromide to form acetoxyhalides (105,106). The formation of acetoxyhalides (105,106) proceed through nucleophilic attack on an intermediate 1,3-dioxolan-2-ylium cation (104) with inversion of configuration. Treatment of the acetoxy halides (105) and (106) under mildly alkaline conditions [K_2CO_3 or Ambelite IRA 410 (OH^-)] affords epoxide (107) in ca. 90% yield. Since both steps can be performed in the same reaction vessel, this reaction sequence provides an extremely efficient method for the direct conversion of 1,2-diols into epoxides with overall retention of configuration [67].

1.5.2.2 Regioselective Sulphonylation

The primary OH group of a diol derived from a terminal olefin can be readily converted to a sulphonate leaving group by treating with arenesulphonyl chloride in the presence of tertiary amine. Under alkaline conditions, hydroxysulphonates are converted to chiral epoxide. The olefin → diol → monosulphonate → epoxide reaction sequence has been applied in a number of natural product and drug syntheses. An example for the usefulness of this sequence is shown in **Scheme 1.12**. 3-(1,2-Dihydroxyethyl)-1,5-dihydro-3H-2,4-benzodioxepine (108), a protected glyceralaldehyde can be obtained in good enantiomeric excess by the dihydroxylation of the corresponding acrolein acetal and recrystallization from benzene. Monotosylation, followed by treatment with sodium methoxide gives glyceraldehydes building block (110) [68].

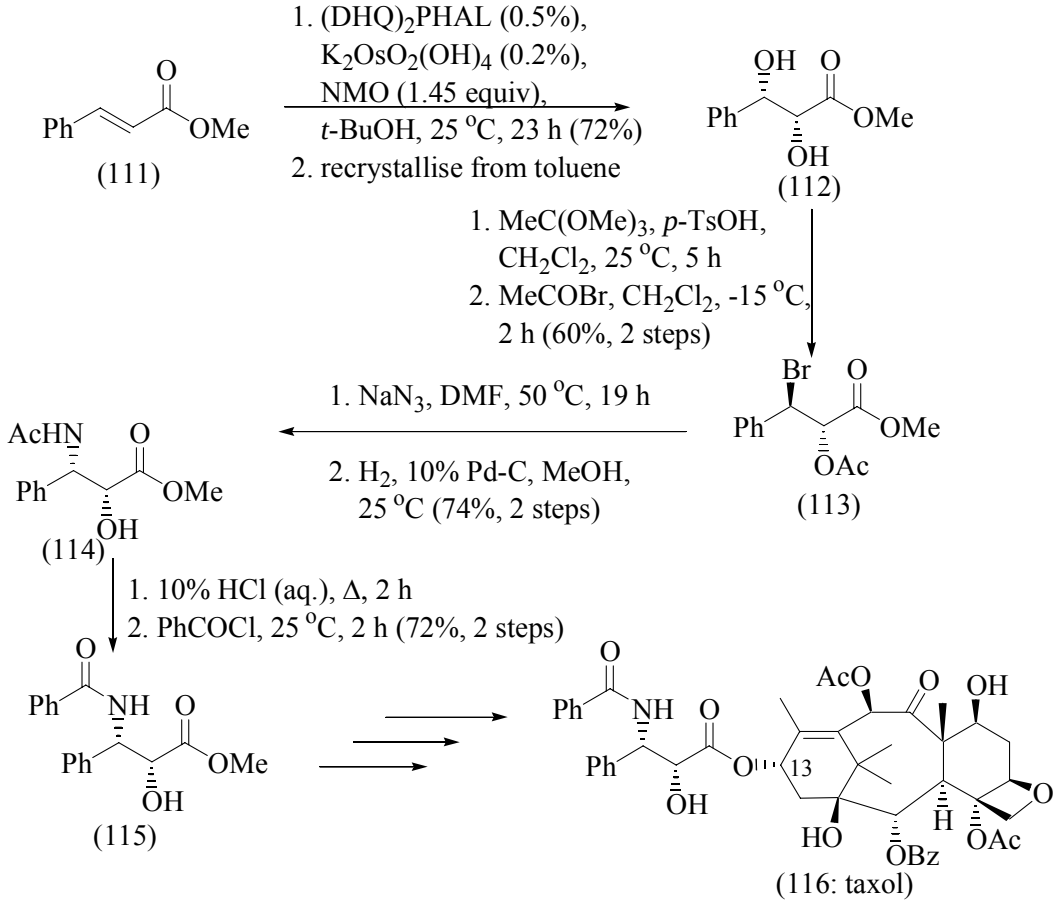


Scheme 1.12: Synthesis of glyceraldehyde building block (110).

1.6 Application of Sharpless AD on the Synthesis of Natural Products

1.6.1 Sharpless's Asymmetric Synthesis of the C-13 Side Chain (115) of Taxol

Since the publication by Sharpless in 1992 [56], more researchers have been using the AD in syntheses, including synthesis of natural products. One of the examples was the Sharpless's asymmetric synthesis of taxol C-13 side chain, as shown in **Scheme 1.13**. Sharpless AD on the methyl cinnamate (111) furnishes the diol (112) in 72% yield and 99% *ee* after recrystallisation. The original secondary oxidant, NMO (84) was used as the co-oxidant instead of $K_3Fe(CN)_6$. This allows the reaction to be run at a very high concentration (2M). The diol (112) was converted to the acetoxybromoester (113) by reaction with trimethyl orthoacetate in the presence of a catalytic amount of *p*-TsOH, followed by treatment with acetyl bromide. The latter step was regioselective (6:1 mixture of the two acetoxybromo esters) favouring the desired product.

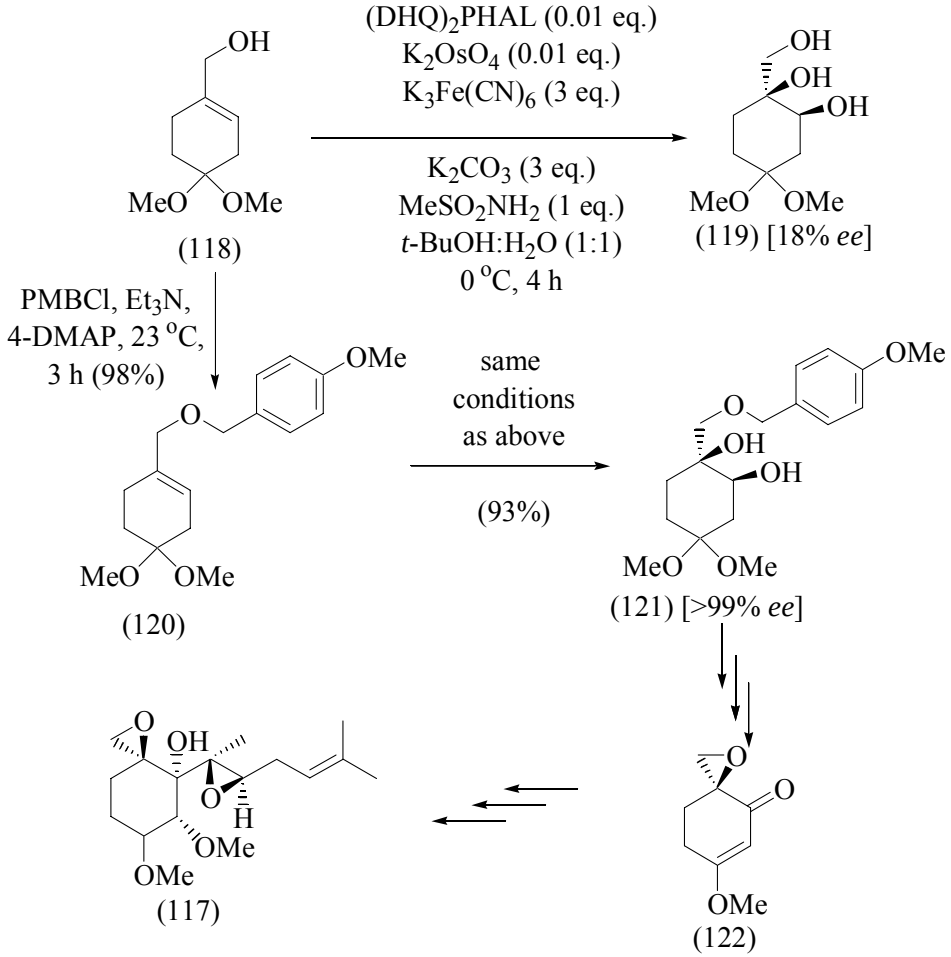


Scheme 1.13: Sharpless's asymmetric synthesis of the C-13 side chain (115) of taxol (116).

The acetoxybromo ester (113) was converted to *N*-acetyl-3-phenylisoserine (114) through displacement of the bromide with azide, followed by hydrogenation of the azide to the amine and *trans*-acylation to afford acetamide (114). Hydrolysis of the acetamide, benzoylation, and hydrolysis of the ester then gives the C-13 side chain (115) of taxol (116) in 23% overall yield from methyl cinnamate (111) [69].

1.6.2 Corey's Total Synthesis of (–)-Ovalicin (117)

Inhibition of angiogenesis, the process of development of new blood vessel, is a potentially valuable medical strategy to prevent the growth of solid tumours by cutting off their blood supply. Ovalicin (117) inhibits angiogenesis has prompted Corey and co-workers to resynthesise ovalicin (117), which has been previously prepared as racemate [70], as shown in **Scheme 1.14**,



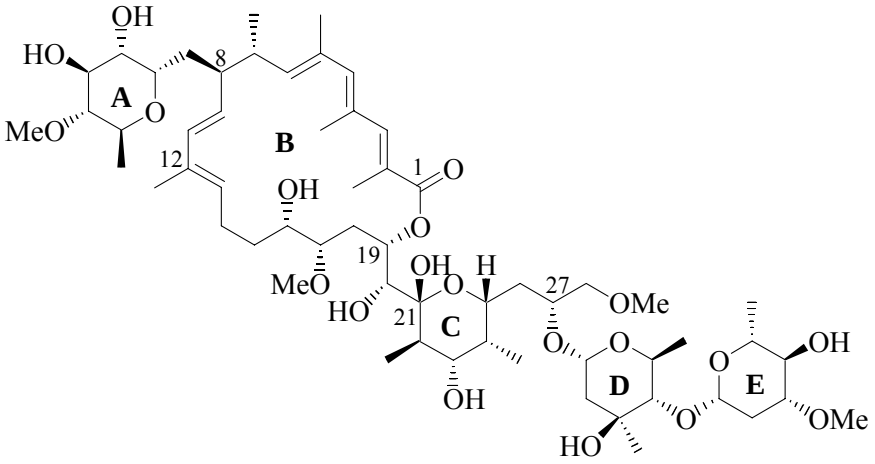
Scheme 1.14: Corey's total synthesis of (–)-ovalicin (117).

Direct AD of (118) with $(DHQ)_2PHAL$ as the chiral ligand gives (119) in only 18% *ee*. However, AD of the *p*-methoxybenzyl ether (120) affords (121) in 93% yield and the *ee* was dramatically increased to more than 99%. This interesting result was attributed to attractive interactions between the PMB group and the aromatic units on the ligand [71]. Enantiomerically pure (121) can be converted to intermediate (122) and thence to (–)-ovalicin (117) by using a previously established pathway [70].

1.6.3 Nicolaou's Total Synthesis of Apoptolidin (123)

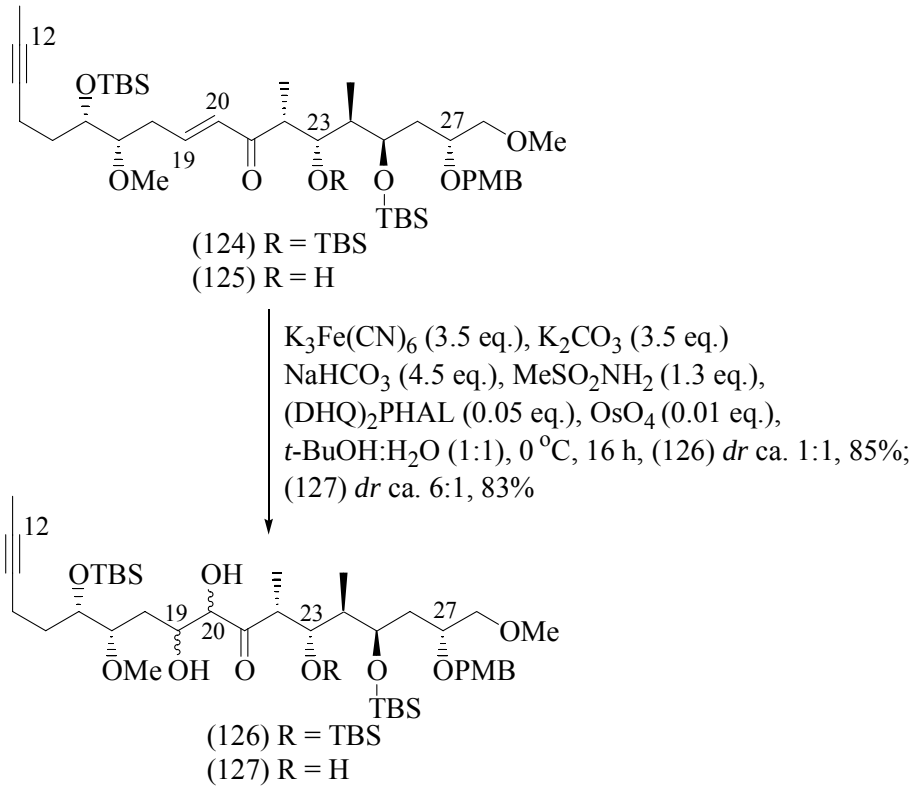
Apoptolidin (123) is a potent apoptolisis-inducing agent isolated from *Nocardiopsis* sp. It has been found to induce apoptotic cell death selectively in rat glia cells transformed with the adenovirus E1A oncogene. In addition, this 20-

membered macrocyclic lactone has also been shown to be an inhibitor of the mitochondrial F_0F_1-ATP synthase. The interesting biological activities and novel structure of apoptolidin (123) prompted Nicolaou and co-workers to synthesise this compound (123) [72-73].



Apoptolidin (123)

AD of α,β-unsaturated ketone (124) is an example of AD of electron-deficient olefins using a buffered AD-mix conditions. The use of buffered condition circumvents problems associated with epimerisation of the α-centre and/or retroaldol fragmentation [74-75]. AD of compound (124) with modified AD-mix-α to form the C_{19}–C_{20} *syn* diol system failed, leading to an inseparable mixture (ca.1:1) of the two possible isomers (126) [72] (**Scheme 1.15**). However, simply removing the TBS protecting group on the C_{23} oxygen dramatically increases the diastereoselectivity of the AD to 6:1. This striking result showed that the substituent on the C_{23} oxygen exerted a strong influence on the dihydroxylation reaction. This interesting result also showed that the stereocontrolling factor (the group on the C_{23} oxygen) is situated four carbon away from the olefinic site where the reaction takes place.

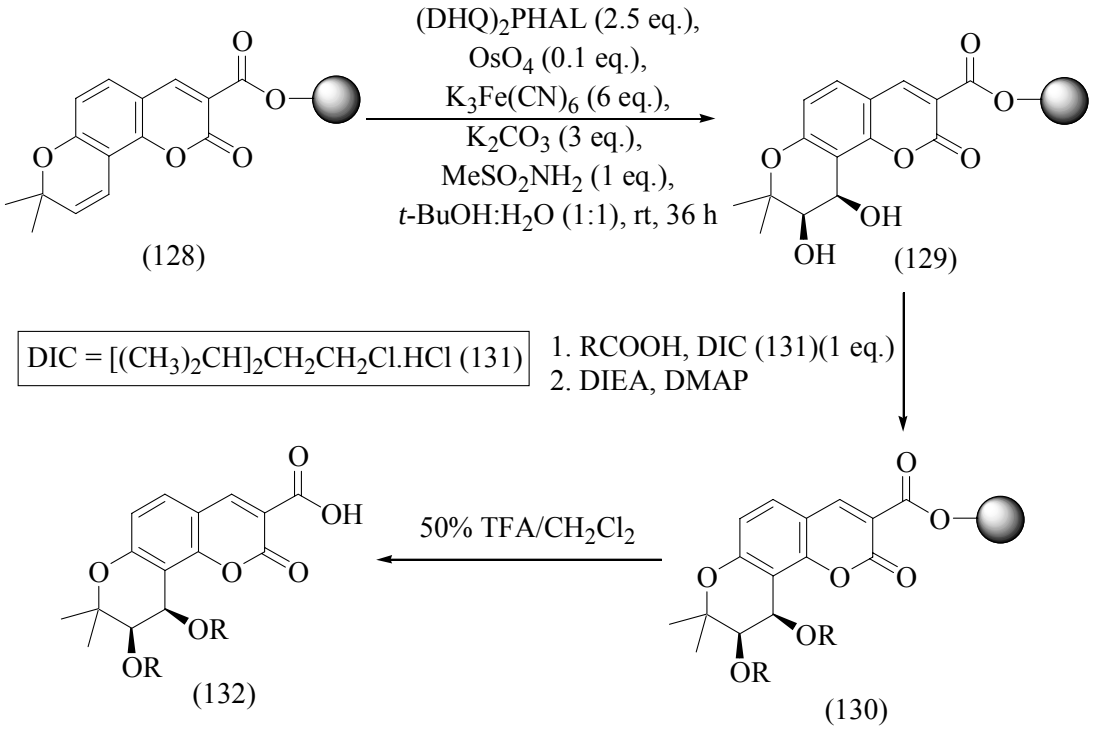


Scheme 1.15: Nicolaou's synthesis of apoptolidin (123).

1.6.4 Solid-Phase Synthesis of (3'*R*,4'*R*)-Di-*O*-*cis*-acyl 3-Carbonyl Khellactones (131)

Solid-phase synthesis of small organic molecules has emerged as an important technology, enabling chemists to synthesise numerous interesting pharmaceutical compounds [76-77]. Although Sharpless AD reactions have been successfully and widely used in the solution phase, AD reactions on solid phase have been reported only infrequently. Lee et al. used Sharpless AD as one of the key steps in solid-phase synthesis of substituted khellactones, as shown in **Scheme 1.16**. Substituted khellactone exhibits a broad range of biological activities, including antifungal, antitumour, antiviral and anti-HIV effects. The resin used in this synthesis was Wang resin. In the AD of the khellactone, resin (128) was subjected to Sharpless AD using $(DHQ)_2$-PHAL as ligand and catalytic OsO_4 to yield (129) in 99% *ee*. The acyl khellactones (130) were synthesised by acylation of the resin (129). Symmetrical anhydrides were prepared from the carboxylic acid using 1 equivalent of DIC (131) in CH_2Cl_2. Resin (129) was treated with excess anhydride in the

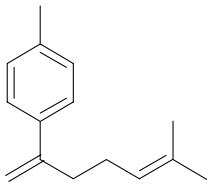
presence of DIEA and DMAP to furnish resin (130). The product (132) was cleaved from the solid support (130) by 50% trifluoroacetic acid in CH_2Cl_2 for 2h [78].



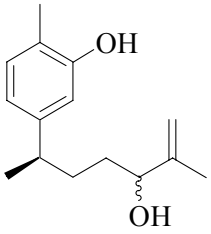
Scheme 1.16: Asymmetric solid-phase synthesis of (3'*R*,4'*R*)-di-*O*-*cis*-acyl 3-carbonyl khellactones (131).

1.7 Xanthorrhizol as Chiral Starting Material for the Synthesis of Natural Products

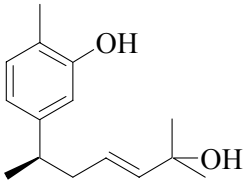
A variety of aromatic bisabolane type natural products is widely distributed, both in terrestrial as well as in marine organisms. In spite of their rather simple structures, some of them have characteristic biological activities. These compounds have attracted synthetic chemists for about 30 years. The parent hydrocarbons (+)-ar-curcumene (3) and dehydro-ar-curcumene (133) are the basic skeleton of aromatic bisabolanes found in many plant essential oils. Examples of the phenolic aromatic bisabolanes are (–)-xanthorrhizol (1), allylic alcohols (134) and (135) [4, 79-80], and the rearranged bisabolane elvirol (136) [81]. More highly oxidised aromatic bisabolanes include triols (137) and (138) [82], (–)-curcuquinone (139), (–)-curcuhydroquinone (140) [83], and gladulone A (141) [84].



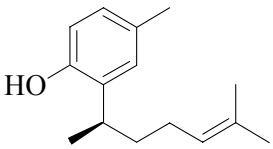
(133)



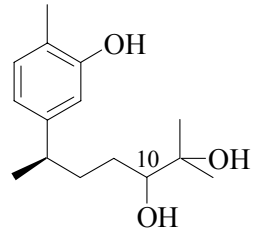
(134)



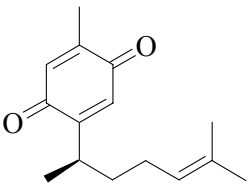
(135)



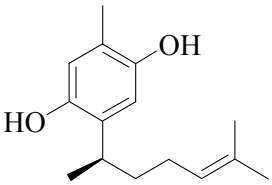
(136)



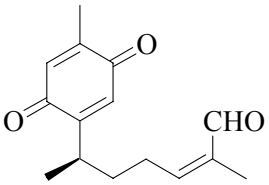
(137) C-10 = *S*
(138) C-10 = *R*



(139)



(140)



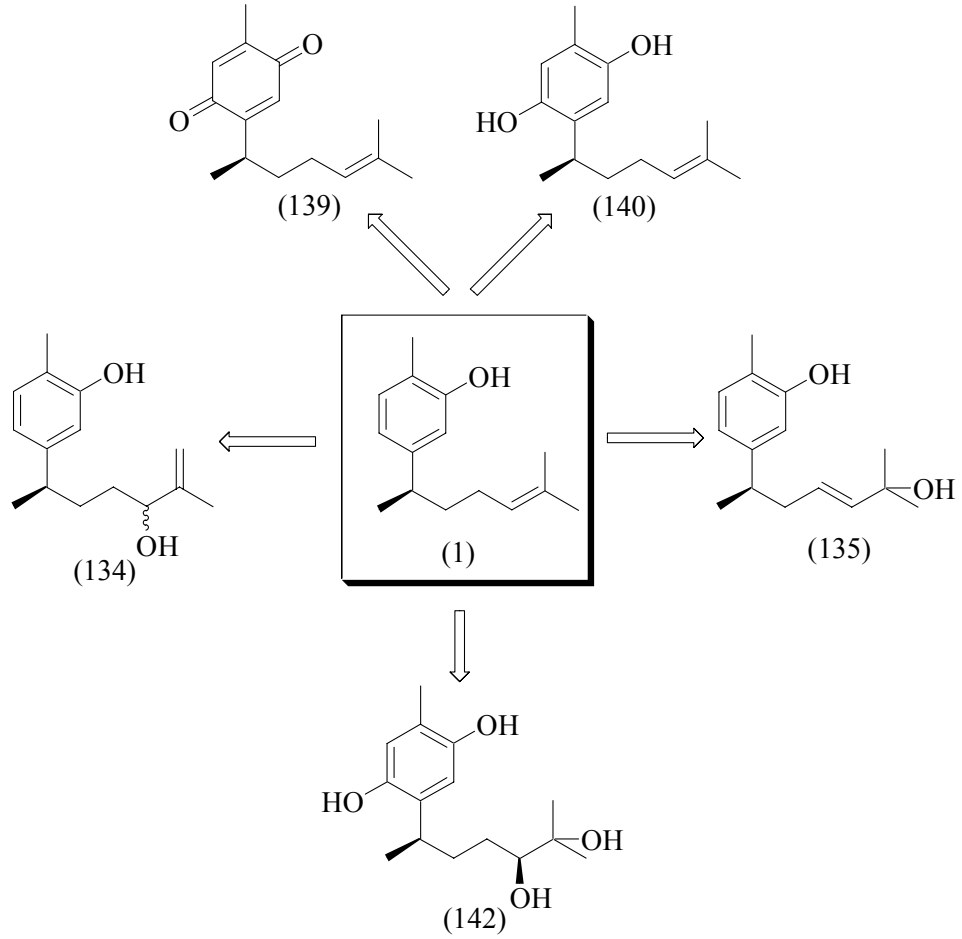
(141)

Although numerous syntheses of racemic phenolic bisabolane type sesquiterpenoids have been known, only a few stereoselective syntheses were reported due to the difficulty of introducing a stereogenic centre in the benzylic position. Besides total synthesis, an alternative way is using natural sesquiterpenoids as starting material for the synthesis of aromatic bisabolane sesquiterpenoids. However, target oriented synthesis of sesquiterpenoids starting from abundantly available natural sesquiterpenoids is a challenging task. It is due to the target molecule which is mostly just one specific molecule and the structural variety in the starting material is often limited. This imposes a double problem and often new or specific methodology has to be developed to achieve such a synthesis.

One of the potential starting materials in this method is xanthorrhizol (1), which is the main component in the essential oil of *C. xanthorrhiza*. Although the synthesis of xanthorrhizol (1) has been extensively studied (see Session 1.4), the difficulties in isolation and supply have limit the studies on the chemistry of this compound. To date, only one report has been published on the chemistry of xanthorrhizol. Aguilar et al. prepared several simple derivatives of xanthorrhizol (1), which displayed mild antifungic activities and did not show cytotoxic activities towards certain human cell lines [85]. Xanthorrhizol (1) used in this study was isolated from the Mexican medicinal plant, *Iostephane heterophylla*. Thus, it is of great interest to study the chemistry of xanthorrhizol (1) in order to exploit the

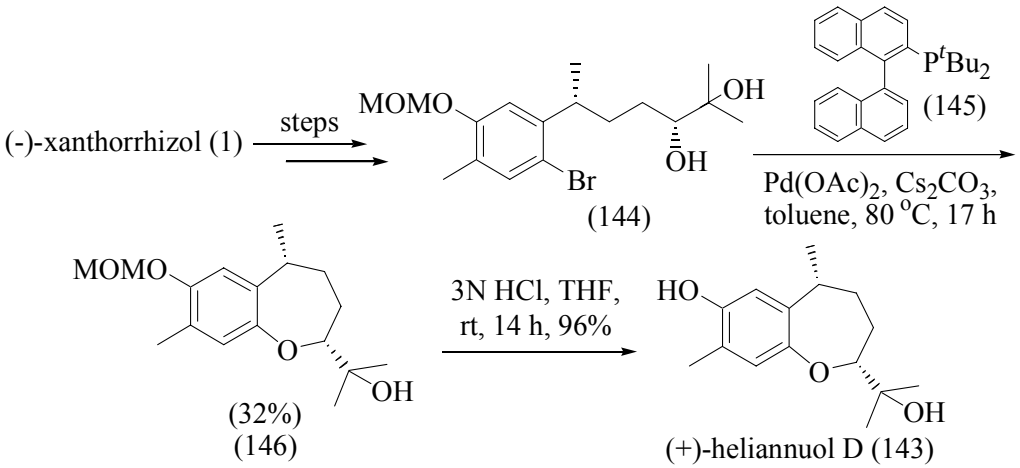
readily available of this compound as a starting material to the other useful compounds.

It is interesting to note that xanthorrhizol (1) is found to be a suitable starting material for the synthesis of several structurally related sesquiterpenoids, *viz* curcuquinone (139), curcuhydroquinone (140), allylic alcohol (134) and (135), helibisabonol A (142) and others as shown in **Scheme 1.17**.



Scheme 1.17: Xanthorrhizol derivatives.

Besides that, xanthorrhizol (1) is a precursor for heliannane type sesquiterpenoids, particularly heliannuol D (143). Shishido and co-workers have prepared heliannuol D (143), an allelochemical, starting from the synthetic *R*-(–)-xanthorrhizol (1) as shown in **Scheme 1.18** [86].



Scheme 1.18: Shishido's synthesis of (+)-heliannuol D (143) from synthetic (–)-xanthorrhizol (1).

The starting material, (–)-xanthorrhizol (1) was previously prepared by the same group (see Session 1.4.5). Xanthorrhizol (1) was subjected to sequential protection, Sharpless AD and bromination to furnish MOM-protected key intermediate (144). Treatment of (144) with palladium acetate (3 mol%) in the presence of *rac*-2-(di-*tert*-butylphosphino)-1,1'-binaphthyl (145) (2.5 mol%) and cesium carbonate in toluene at 80 °C produced the desired aryl ether (146) in 32% yield. Acidic hydrolysis of compound (146) with 3N HCl in THF afforded (+)-heliannuol D (143) in 96% yield.

Heliannuol D (143) has been isolated by Macías from the moderately polar active fractions of the leaf aqueous extract of sunflowers (*Helianthus annuus* L. SH-222). Heliannuol D (143) has been found to be a promising group of phenolic allelochemicals that exhibit activity against dicotyledon plant species [87].

Allelopathy is a brand of science, which studies biochemical plant-plant and plant-microorganism interactions. Allelopathy is most commonly defined as any direct or indirect effect (stimulatory or inhibitory) by one plant, including microorganisms, on another plant or microorganism through the production of chemical compounds released into the environment [88]. Allelochemicals have been implicated as biocommunicators and are an important potential source for new herbicides and agrochemicals [89].

1.8 Objectives

The first objective is to isolate xanthorrhizol (1) from the essential oil of *C. xanthorrhiza* by VLC purification. The second goal is to convert xanthorrhizol (1) to several bisabolane-type sesquiterpenoids, *viz*. both diastereomers of 10,11-dihydro-10,11-dihydroxyxanthorrhizols (137,138), curcuquinone (139), curcuhydroquinone (140), helibisabonol A (142) and allylic alcohol derivative of *O*-methylxanthorrhizol (147), as shown in the flow chart (**Figure 1.2**).

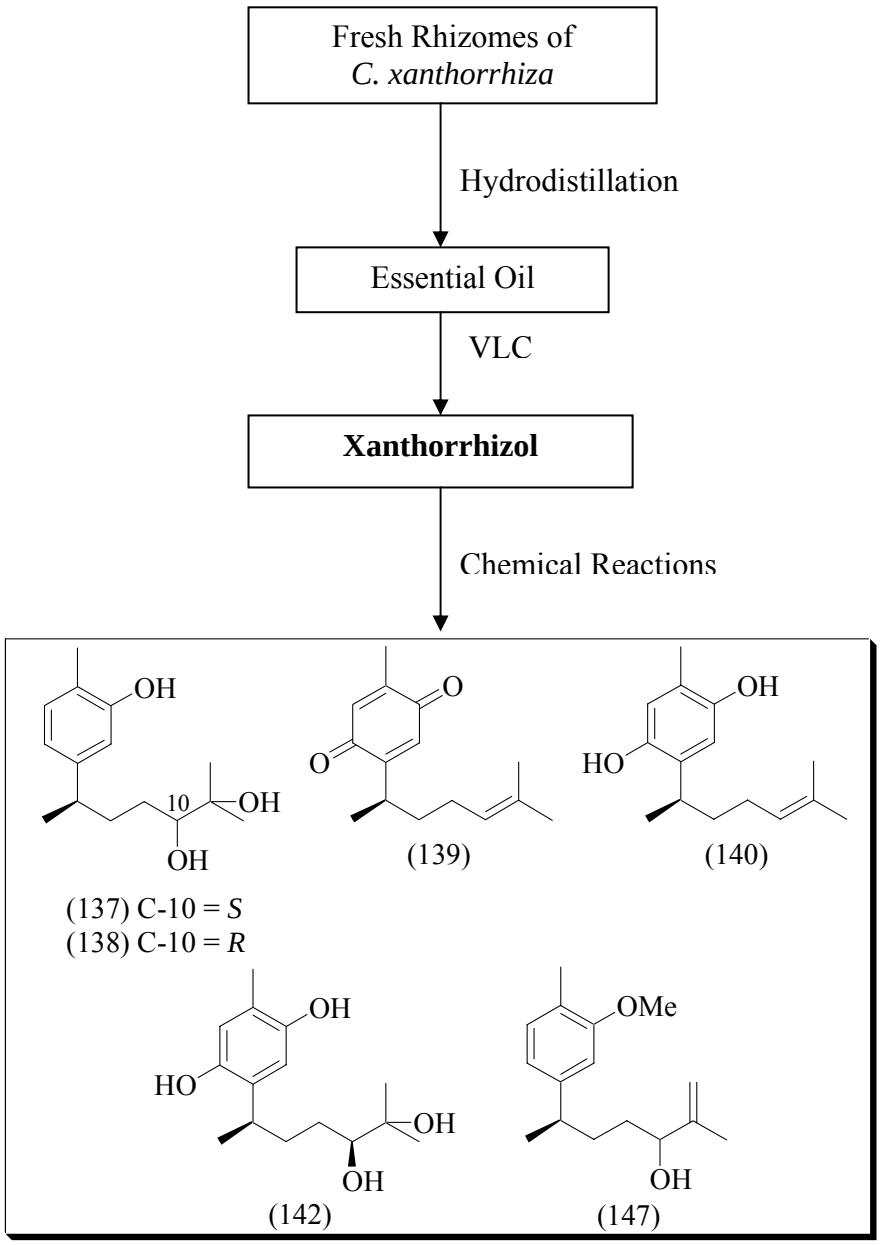


Figure 1.2: Isolation of xanthorrhizol (1) and transformation of xanthorrhizol (1) to several bisabolane type sesquiterpenoids.