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## RECENT ADVANCES IN THE SYNTHESSES OF DECALIN TYPE NATURAL PRODUCTS

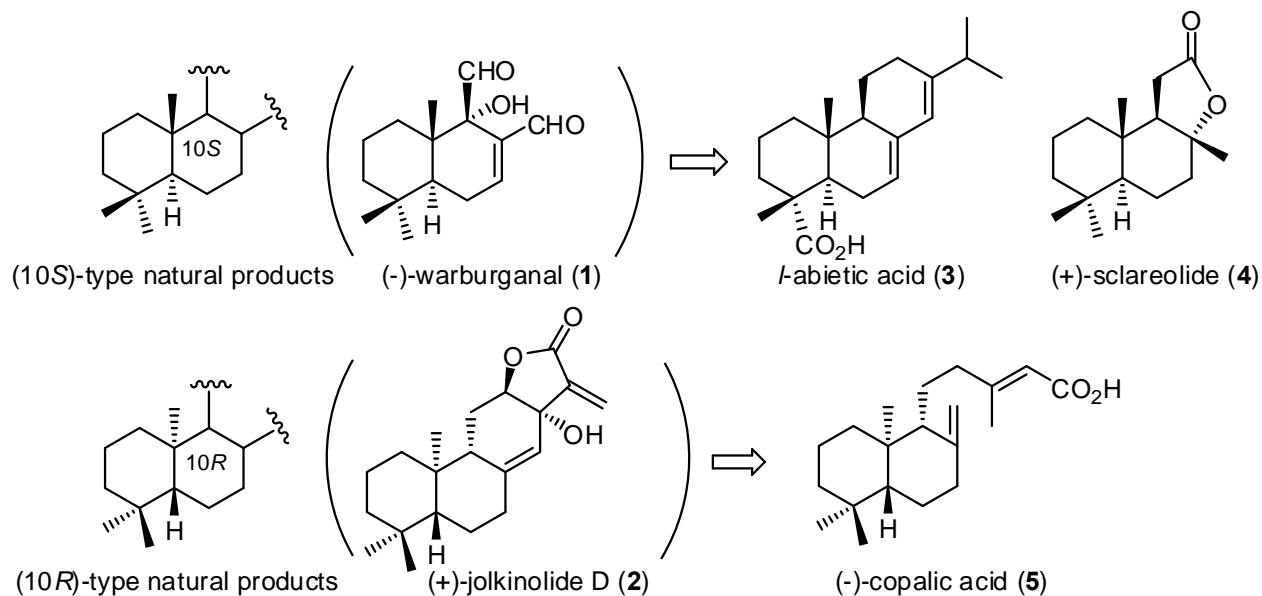
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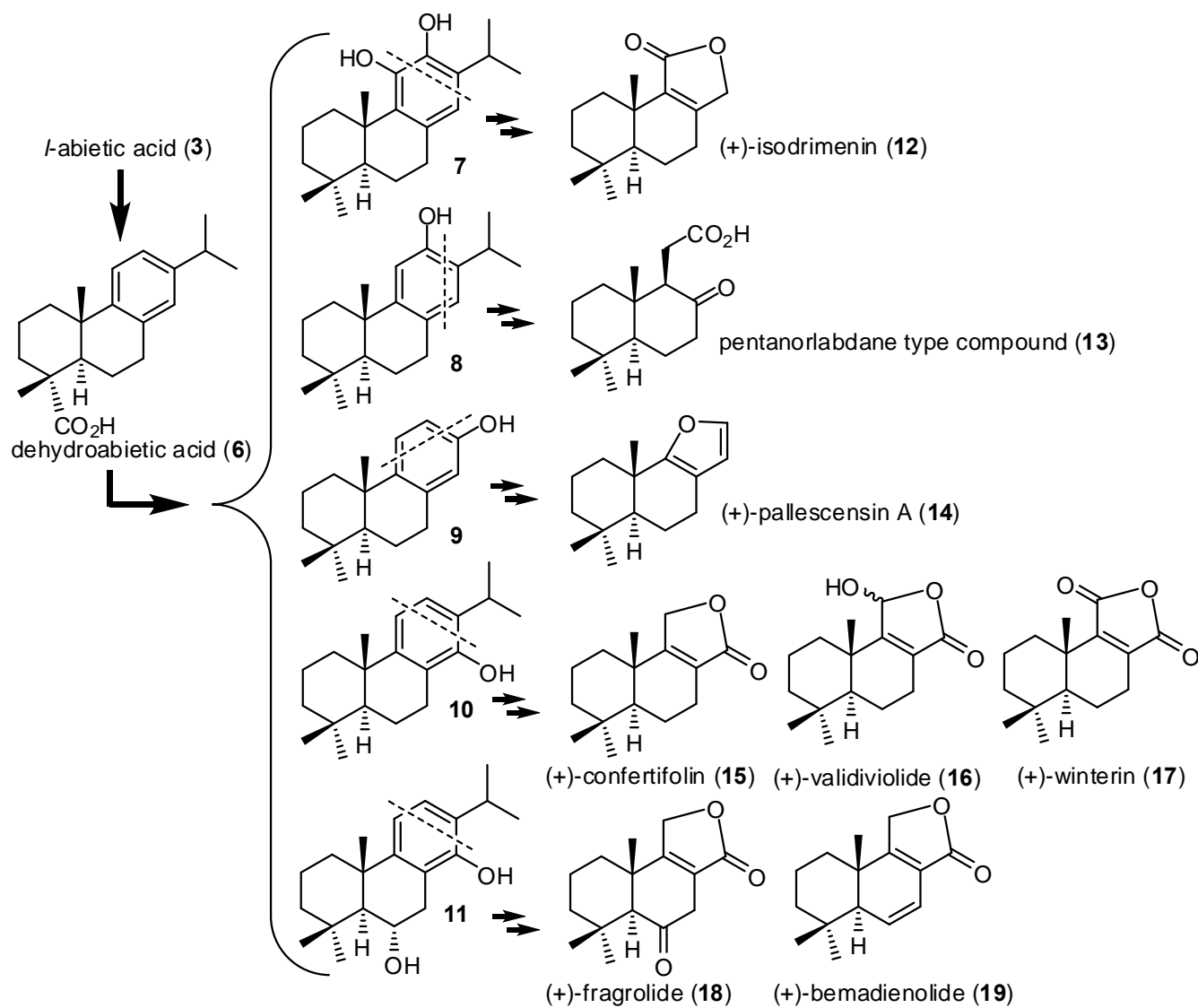
**Abstract** – This review summarizes the practical synthesis of both enantiomers of chiral intermediate for the syntheses of the natural products possessing the bicyclo[4.4.0]ring system with 4,4,10-trimethyl groups and their application to the total syntheses of the related natural products. Chiral induction was carried out based on enzymatic resolution or optical resolution using chiral auxiliary.

### 1. Introduction

Numerous syntheses of the natural products possessing the bicyclo[4.4.0]ring system with 4,4,10-trimethyl groups have reviewed within the last forty years and synthesis has been accomplished by the transformation of other natural products or by total syntheses.<sup>1,2</sup> Chiral compounds possessing the bicyclo[4.4.0]ring system with 4,4,10-trimethyl groups are an important requisite found in a variety of natural products like drimane sesquiterpenoids and other related natural compounds. In these chiral compounds, there are many biologically active (10*S*)-type natural products such as (-)-warburganal (**1**) and (10*R*)-type natural products such as (+)-jolkinolide D (**2**) as shown in Scheme 1. The former type natural products could be synthesized from natural source such as *l*-abietic acid (**3**) or (+)-sclareolide (**4**), while the latter type natural products could be derived from natural source such as (-)-copalic acid (**5**). In the course of our studies on the chemical conversion of *l*-abietic acid (**3**) to optically active natural products,<sup>3</sup> ozonolysis of phenolic compounds [11,12-dihydroxy dehydroabietane (**7**),<sup>4</sup> ferruginol (**8**),<sup>4</sup> 13-hydroxy-13-deisopropyldehydroabietane (**9**),<sup>4</sup> 14-hydroxydehydroabietane (**10**),<sup>4</sup> and 6 $\alpha$ ,14-dihydroxydehydroabietane (**11**)<sup>5</sup>] derived from dehydroabietic acid (**6**) followed by reduction or/and oxidation with the appropriate reagent afforded (+)-isodrimenin (**12**),<sup>5,6</sup> pentanorlabdane type compound (**13**),<sup>5,6</sup> (+)-pallescensin A (**14**),<sup>5,6</sup> (+)-confertifolin (**15**),<sup>5,6</sup> (+)-valdiviolide (**16**),<sup>5,6</sup> (+)-winterin (**17**),<sup>5,6</sup> (+)-fragrolide (**18**),<sup>5,7</sup> and (+)-bemadienolide (**19**),<sup>5,7</sup> respectively, as shown in Scheme 2.

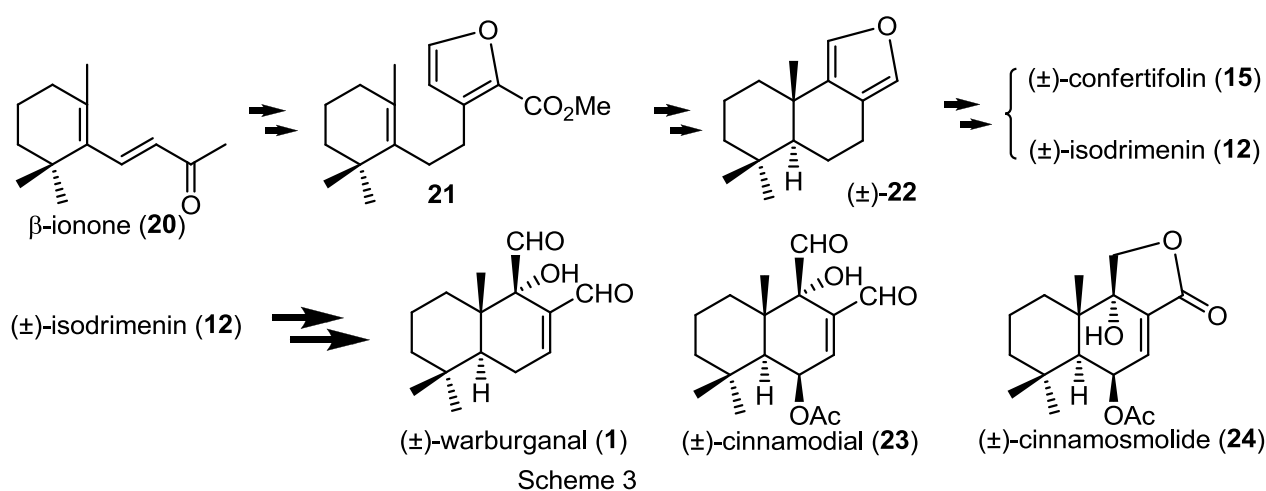


Scheme 1



Scheme 2

The mode of cleavage was governed by the substitution pattern of the hydroxyl group on the aromatic ring. On the other hand, a large scale synthesis of ( $\pm$ )-**12** and ( $\pm$ )-**15** was achieved from the starting  $\beta$ -ionone (**20**) as shown in Scheme 3.<sup>8,9</sup> The cyclization of the furanic ester **21** followed by saponification and decarboxylation afforded ( $\pm$ )-euryfuran (**22**). Further transformations of the furan ring provided the drimane sesquiterpenoids ( $\pm$ )-**12**, ( $\pm$ )-**15**, ( $\pm$ )-**1**,<sup>10,11</sup> ( $\pm$ )-cinnamodial (**23**),<sup>12,13</sup> and ( $\pm$ )-cinnamosmolide (**24**).<sup>12,13</sup> In this review, we describe the practical synthesis of both enantiomers of chiral intermediate for the syntheses of the natural products possessing the bicyclo[4.4.0]ring system with 4,4,10-trimethyl groups and their application to the total syntheses of the related compounds. Chiral induction was carried out based on enzymatic resolution or optical resolution using chiral auxiliary.

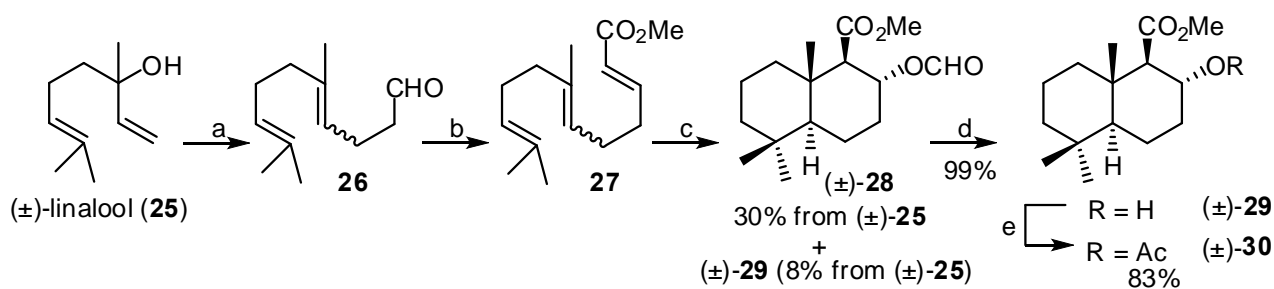


## 2. SYNTHESIS OF BOTH ENANTIOMERS OF CHIRAL SYNTHON AND THEIR APPLICATION TO THE SYNTHESSES OF THE NATURAL PRODUCTS POSSESSING THE BICYCLO[4.4.0]RING SYSTEM WITH 4,4,10-TRIMETHYL GROUPS

### 2.1. Lipase assisted hydrolysis or esterification of the racemic methyl (1 $\beta$ ,2 $\alpha$ ,4 $\alpha$ ,8 $\alpha\beta$ )-2-hydroxydecahydro-5,5,8a-trimethylnaphthalene-1-carboxylate and its congener

Optically active title compound (**29**) was considered to be an important chiral intermediate for the synthesis of drimane type natural products and the racemic substrate for enzymatic resolution was synthesized from ( $\pm$ )-linalool (**25**) as shown in Scheme 4.<sup>14</sup> Heating of **25** and ethyl vinyl ether in the presence of H<sub>3</sub>PO<sub>4</sub> followed by acid treatment gave a mixture of aldehyde (**26**), which was reacted with Wittig reagent to afford the methyl  $\Delta^2$  *trans*-dodecatrienoate (**27**). Biomimetic cyclization of **27** in HCOOH-H<sub>2</sub>SO<sub>4</sub> yielded the ( $\pm$ )-formate (**28**) and  $\beta$ -hydroxy ester ( $\pm$ )-**29** in 30% and 8% overall yield from ( $\pm$ )-**25**, respectively. Saponification of ( $\pm$ )-**28** gave quantitatively ( $\pm$ )-**29**, which was treated with

Ac<sub>2</sub>O in pyridine to provide the acetate (±)-**30**. When the β-acyloxy esters (±)-**28** and (±)-**30** were exposed to the immobilized lipase OF-360 from *Candida rugosa* in a water-saturated organic solvent, the hydrolyzed product (8a*S*)-**29** was obtained in moderate chemical (40~27%) and high optical (>99% ee) yields. On the other hand, enzymatic acetylation of (±)-**29** and vinyl acetate in the presence of the same lipase gave 89% ee of (8a*S*)-**30** in 9% yield as shown in Scheme 4. From this experiment, conversion rate using lipase was found to be late. Then enantioselective and regioselective acetylation of the (±)-1,3-diol (**31**) obtained from LiAlH<sub>4</sub> reduction of (±)-**29** was carried out as shown in Scheme 5. Exposure of (±)-**31**

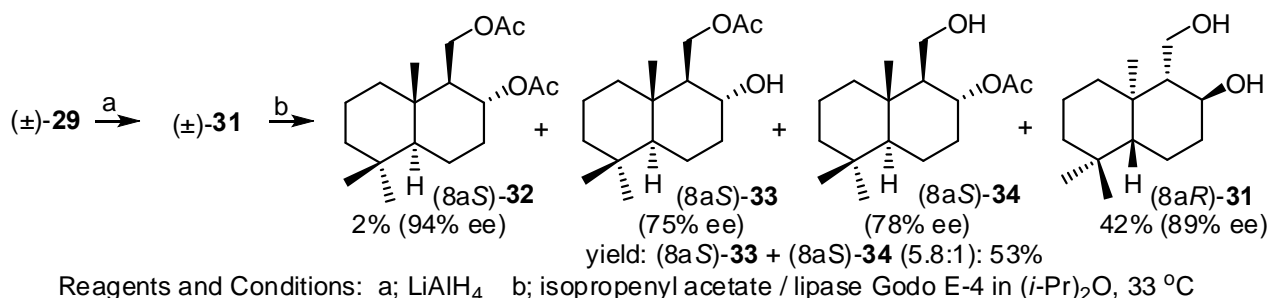


Reagents: a; 1) ethyl vinyl ether / H<sub>3</sub>PO<sub>4</sub> 2) 10% aq. AcOH b; Ph<sub>3</sub>P=CHCO<sub>2</sub>Me c; HCO<sub>2</sub>H / H<sub>2</sub>SO<sub>4</sub>  
 d; K<sub>2</sub>CO<sub>3</sub> / MeOH e; Ac<sub>2</sub>O / pyridine



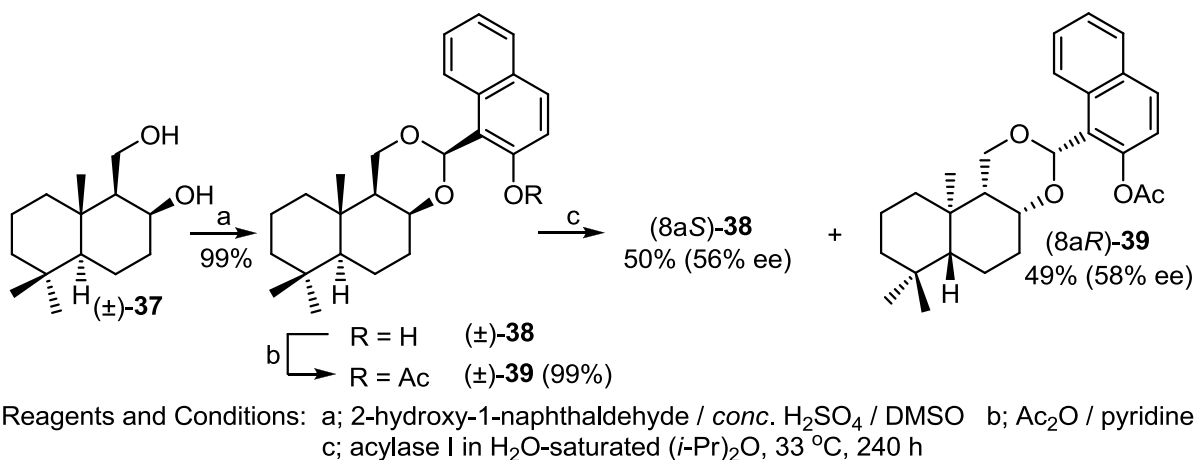
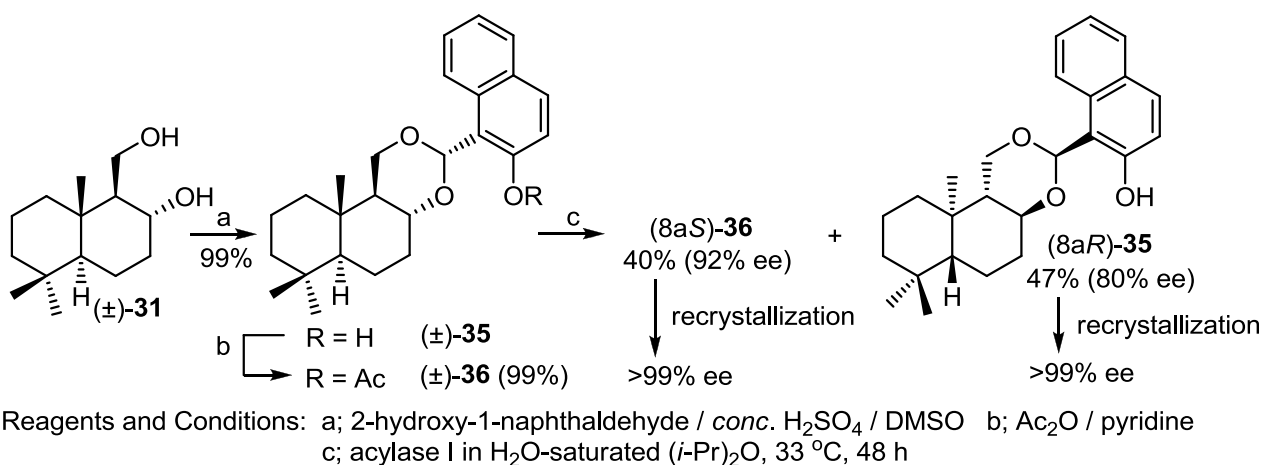
Scheme 4

with isopropenyl acetate in the presence of the lipase Godo E-4 from *Pseudomonas* sp. provided four kinds of optically active compounds (8a*S*)-**32** (94% ee), (8a*S*)-**33** (75% ee), (8a*S*)-**34** (78% ee) and (8a*R*)-**31** (89% ee) because (±)-**31** has two reaction sites for acetylation.<sup>14</sup> This problem could be overcome by converting two reaction sites to one reaction site in the substrate. This synthetic strategy could be realized by the formation of a phenolic acetal (±)-**35** which corresponds to the masked 1,3-diol



Scheme 5

structure. The newly introduced bulky naphthyl group in the substrate  $(\pm)\text{-35}$  situated with the thermodynamically stable equatorial conformation. The reaction of  $(\pm)\text{-31}$  and 2-hydroxy-1-naphthaldehyde gave the phenolic acetal  $(\pm)\text{-35}$  as a single diastereomer in quantitative yield whose acetylation afforded the corresponding acetate  $(\pm)\text{-36}$  in 99% yield as shown in Scheme 6.<sup>15</sup> From a screening experiment using various kinds of lipase and acylase, a commercially available acylase I (No. A-2156) from *Aspergillus melleus* was found to be effective. When the phenolic acetate  $(\pm)\text{-36}$  was

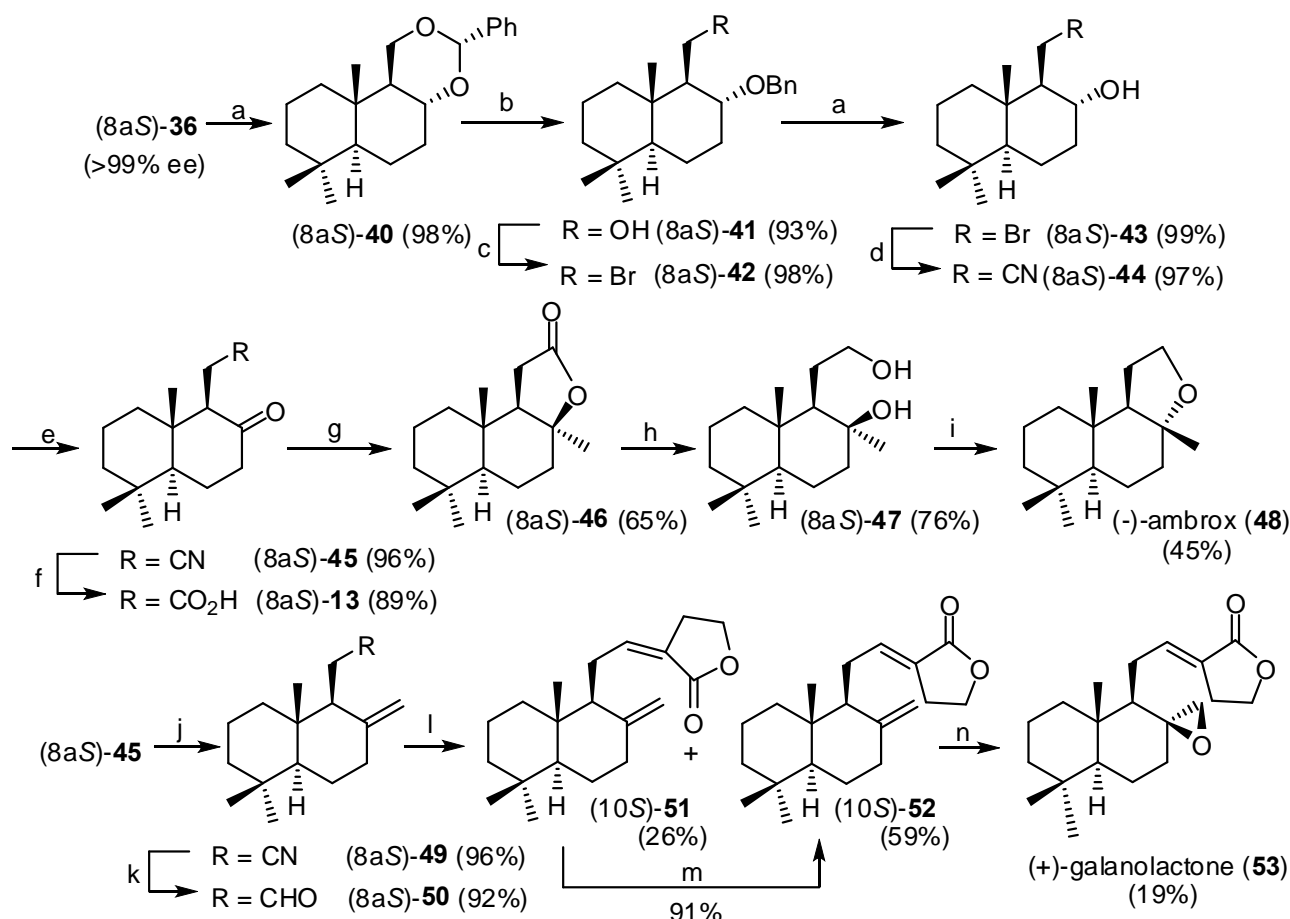


Scheme 6

exposed to the acylase I in water-saturated diisopropyl ether, hydrolyzed product (8aR)-**35** (47%, 80% ee) and unchanged (8aS)-**36** (40%, 92% ee) were obtained. An enantiomeric excess of both materials was improved to give enantiomerically pure (8aR)-**35** and (8aS)-**36** by recrystallization, respectively. On the other hand, ( $\pm$ )-*cis*-1,3-diol (**37**) obtained from oxidation of ( $\pm$ )-**29** followed by LiAlH<sub>4</sub> reduction was converted to the phenolic acetate ( $\pm$ )-**39** by the same way as the preparation of ( $\pm$ )-**36** as shown in Scheme 6.<sup>16</sup> When the phenolic acetate ( $\pm$ )-**39** was exposed to the acylase I in water-saturated diisopropyl ether, hydrolyzed product (8aS)-**38** (50%, 56% ee) and unchanged (8aR)-**36** (49%, 58% ee) were obtained. It was found that steric recognition by lipase was opposite between ( $\pm$ )-**36** and ( $\pm$ )-**39**.

## 2.2. Synthesis of (-)-ambrox and (+)-galanolactone

(-)-Ambrox (**48**) is a perfume and synthesized from the present enzymatic product (8aS)-**36** as shown in Scheme 7.<sup>15</sup> A catalytic hydrogenation of (8aS)-**36** followed by treatment with benzaldehyde in the presence of a catalytic amount of acid afforded an acetal (8aS)-**40** exclusively in 98% yield. Reduction of



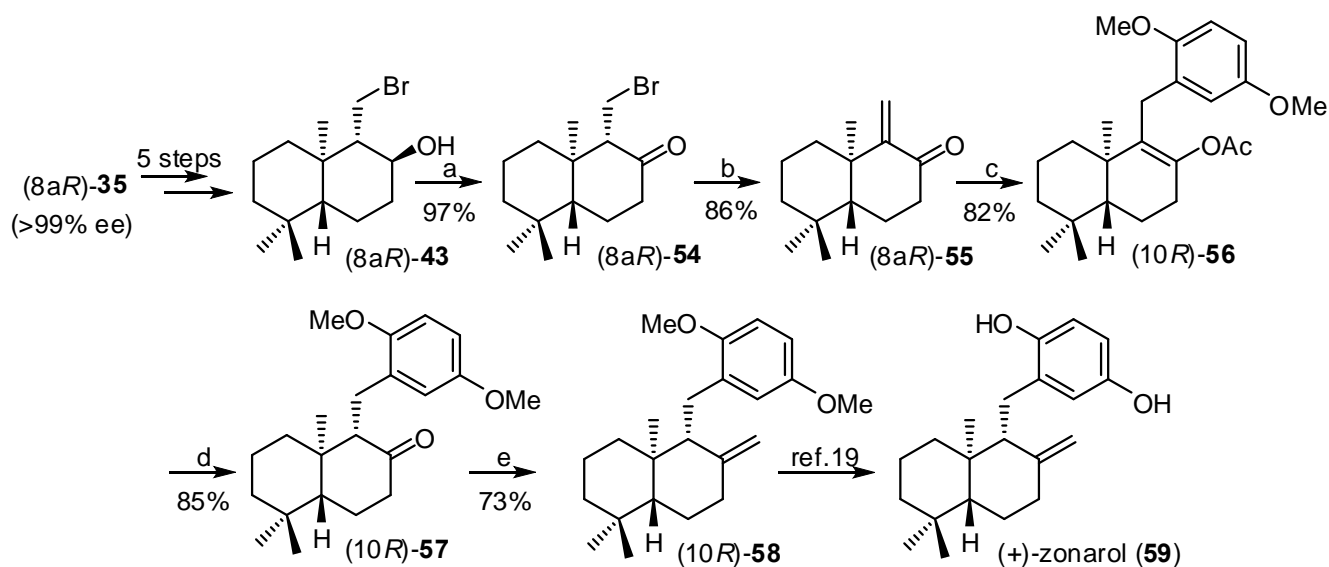
Reagents : a; 1) H<sub>2</sub>, 20% Pd(OH)<sub>2</sub>-C / AcOEt 2) PhCHO / *conc.* H<sub>2</sub>SO<sub>4</sub> / DMSO  
 b; LiAlH<sub>4</sub> (1 eq.) / AlCl<sub>3</sub> (4 eq.) / Et<sub>2</sub>O c; CBr<sub>4</sub> / Ph<sub>3</sub>P / THF d; NaCN / DMSO  
 e; Jones reagent / acetone f; 1) NaOH / H<sub>2</sub>O / MeOH 2) 2M HCl g; 1) MeLi / THF-Et<sub>2</sub>O 2) *p*-TsOH  
 h; LiAlH<sub>4</sub> / Et<sub>2</sub>O i; *p*-TsOH / MeNO<sub>2</sub> j; Ph<sub>3</sub>P<sup>+</sup>Me Br / NaNH<sub>2</sub> / toluene k; HAl(*i*-Bu)<sub>2</sub> / toluene  
 l; diethylphosphono-2-butyrolactone, NaOMe / MeOH m; hv, (PhS)<sub>2</sub> / benzene n; *m*-CPBA / CHCl<sub>3</sub>

Scheme 7

(8a*S*)-**40** with a mixed reducing reagent [LiAlH<sub>4</sub> (1 equiv.)-AlCl<sub>3</sub> (4 equiv.)] provided selectively primary alcohol (8a*S*)-**41** (93%), which was treated with CBr<sub>4</sub> and Ph<sub>3</sub>P to give the bromide (8a*S*)-**42** in 98% yield. A catalytic hydrogenation of (8a*S*)-**42** followed by treatment with NaCN provided nitrile (8a*S*)-**44** in 96% overall yield. Oxidation of (8a*S*)-**44** with Jones reagent followed by acidic hydrolysis gave the β-keto acid (8a*S*)-**13** in 85% overall yield. Reaction of (8a*S*)-**13** with MeLi followed by treatment with *p*-TsOH provided the γ-lactone (8a*S*)-**46** (65%). Reduction of (8a*S*)-**46** with LiAlH<sub>4</sub> yielded the diol (8a*S*)-**47** (76%), which was treated with *p*-TsOH in MeNO<sub>2</sub> provided the (-)-ambrox (**48**) in 45% yield. (+)-Galanolactone (**53**) is reported to exhibit anti-5HT (serotonin) effect and synthesized from the keto nitrile (8a*S*)-**45** as shown in Scheme 7.<sup>17</sup> Wittig olefination of (8a*S*)-**45** with Ph<sub>3</sub>P=CH<sub>2</sub> provided the exo-olefin (8a*S*)-**49** (96%), which was reduced with Dibal-H to provide an aldehyde (8a*S*)-**50** (92%). Coupling of (8a*S*)-**50** with the anion of diethylphosphono-2-butyrolactone afforded the isomeric lactones (10*S*)-**51** (*Z*-form, 26% yield) and (10*S*)-**52** (*E*-form, 59% yield). Isomerization of (10*S*)-**51** to (10*S*)-**52** was effected by irradiation in the presence of diphenyl disulfide and 91% conversion yield of (10*S*)-**52** was achieved. By applying the reported procedure,<sup>18</sup> epoxidation of exo-olefin group of (10*S*)-**52** with *m*-CPBA gave (+)-galanolactone (**53**) in 19% yield.

### 2.3. Formal synthesis of (+)-zonarol

A formal total synthesis of (+)-zonarol (**59**) from enzymatic product (8a*R*)-**35** was then carried out as shown in Scheme 8.<sup>15</sup> The (8a*R*)-**35** was converted into the 1,3-bromohydrin (8a*R*)-**43** in 88% overall yield in the same way as in the conversion of (8a*S*)-**36** to (8a*S*)-**43**. Oxidation of (8a*R*)-**43** gave the



Reagents : a; Jones reagent / acetone b; DBU / benzene c; 1) 2,5-dimethoxyphenylmagnesium bromide, CuI / THF 2) Ac<sub>2</sub>O d; KOH / MeOH e; Ph<sub>3</sub>P<sup>+</sup>Me Br<sup>-</sup> / n-BuLi / THF

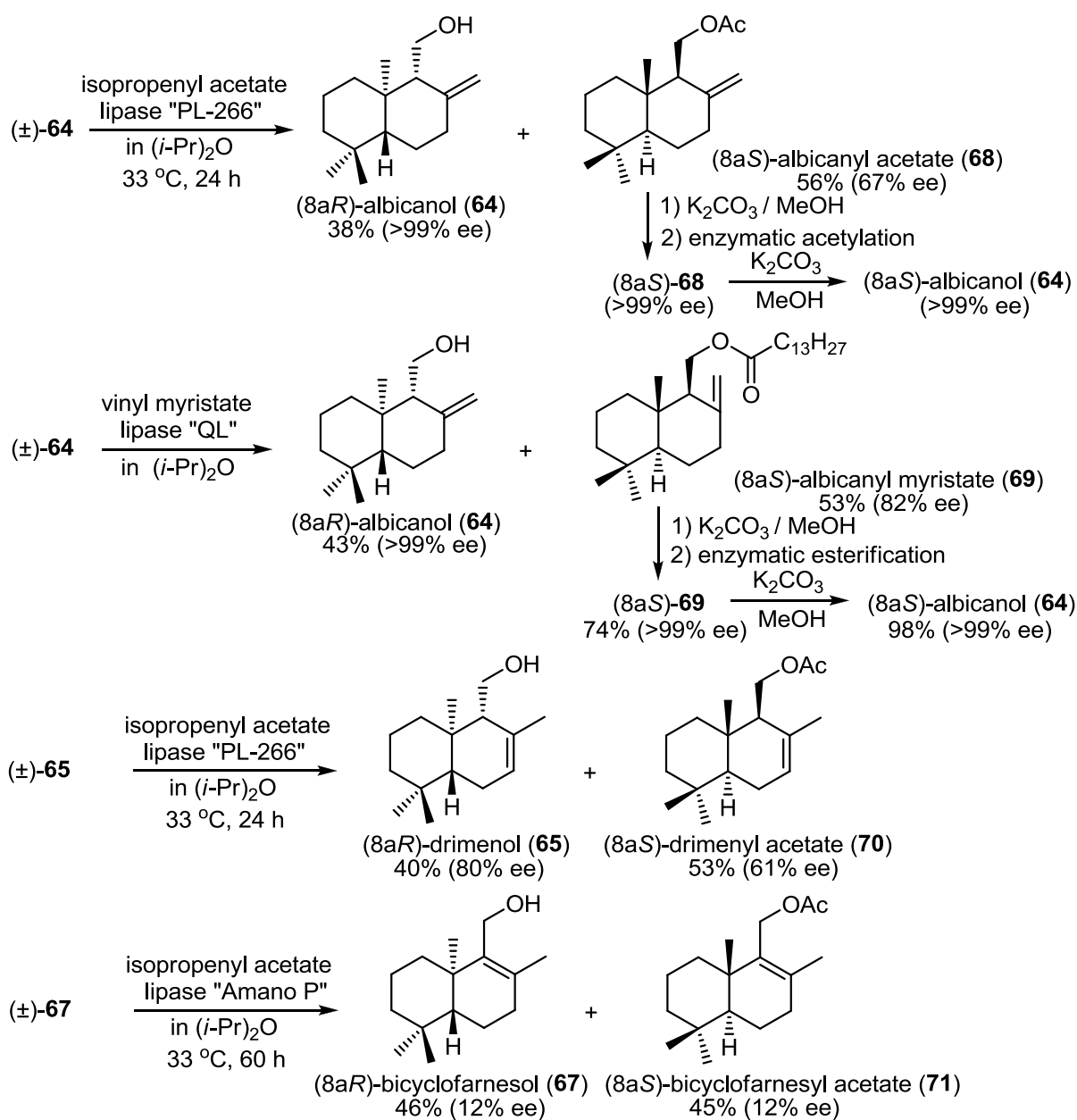
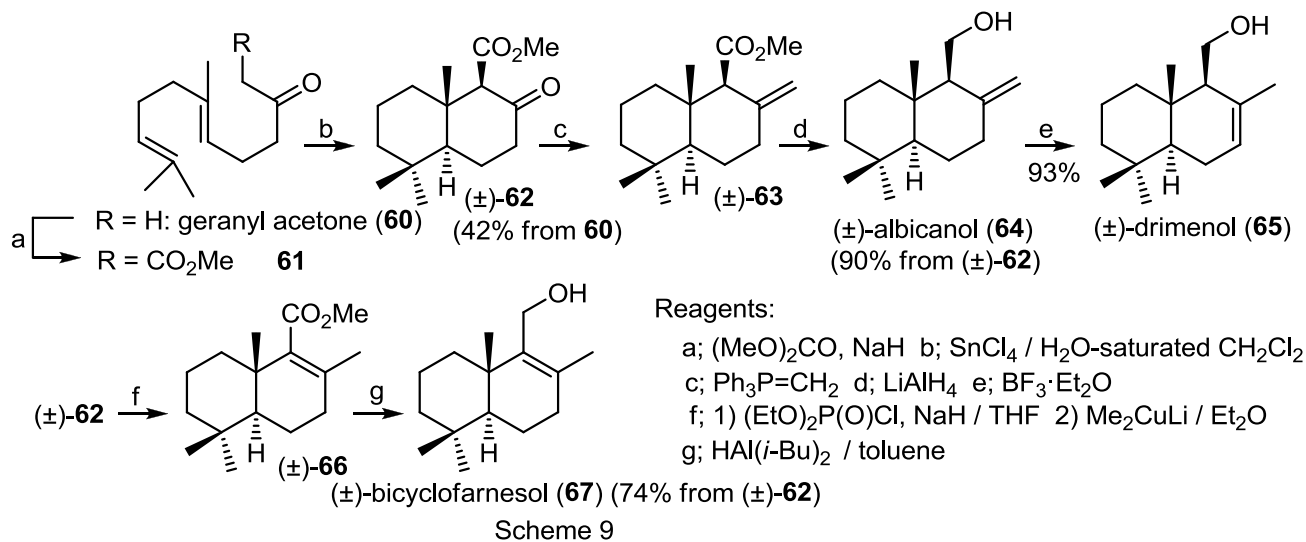
Scheme 8

bromo-ketone (8aR)-**54** in 97% yield, which was treated with DBU to afford the  $\alpha,\beta$ -unsaturated ketone (8aR)-**55** in 86% yield. Michael addition of (8aR)-**55** with the 2,5-dimethoxyphenyl Grignard reagent in the presence of CuI followed by treatment with Ac<sub>2</sub>O provided an enol acetate (10R)-**56** in 82% yield, which was hydrolyzed to the ketone (10R)-**57** in 85% yield. Wittig reaction of (10R)-**57** with phosphonium salt in the presence of *n*-BuLi afforded the exo-olefin (10R)-**58** (73% yield) whose spectral data were identical with those of the reported olefin (10R)-**58**.<sup>19</sup> Total synthesis of (+)-zonarol (**59**) from (10R)-**58** has been already achieved.<sup>19</sup>

### 3. SYNTHESIS OF BOTH ENANTIOMERS OF ALBICANOL AND THEIR APPLICATION TO THE SYNTHESSES OF THEIR RELATED NATURAL PRODUCTS

#### 3.1. Lipase assisted esterification of the racemic albicanol, drimenol and bicyclofarnesol

The substrates [(±)-albicanol (**64**), (±)-drimenol (**65**) and (±)-bicyclofarnesol (**67**)] for enzymatic reaction were synthesized from geranyl acetone (**60**) as shown in Scheme 9.<sup>20,21</sup> The reaction of **60** and dimethyl carbonate in the presence of NaH gave the  $\beta$ -keto ester (**61**), which was subjected to biomimetic cyclization to afford the (±)-cyclic  $\beta$ -keto ester (**62**) in 42% overall yield from **60**. Wittig olefination of (±)-**62** followed by reduction gave (±)-**64** in 90% overall yield from (±)-**62**. BF<sub>3</sub>·Et<sub>2</sub>O assisted isomerization of (±)-**64** selectively gave (±)-**65** in 93% yield. On the other hand, the reaction of (±)-**62** with diethyl chlorophosphate followed by treatment with Me<sub>2</sub>CuLi yielded the  $\alpha,\beta$ -unsaturated ester (±)-**66**, which was reduced with Dibal-H to afford (±)-**67** in 74% overall yield from (±)-**62**. Then, enzymatic esterification of thus obtained (±)-**64**, (±)-**65** and (±)-**67** was carried out as shown in Scheme 10. Enzymatic acetylation of (±)-**64** in the presence of isopropenyl acetate and lipase “PL-266” gave (8aR)-**64** (>99% ee, 38% yield) and an acetate (8aS)-**68** (67% ee, 57% yield). The 67% ee of (8aS)-**68** was hydrolyzed followed by repeated acetylation to afford the optically pure (8aS)-**68**.<sup>20</sup> This enzymatic esterification was improved by exchange of acylating reagent.<sup>21</sup> Enzymatic esterification of (±)-**64** in the presence of vinyl myristate and lipase “QL” gave (8aR)-**64** (>99% ee, 43% yield) and the myristate (8aS)-**69** (82% ee, 53% yield). The 82% ee of (8aS)-**69** was hydrolyzed followed by repeated acylation to afford the optically pure (8aS)-**69** in 74% overall yield. Hydrolysis of (8aS)-**69** (>99% ee) with K<sub>2</sub>CO<sub>3</sub> in MeOH gave the optically pure (8aS)-**64** (98%). Enzymatic acetylation of (±)-**65** in the presence of isopropenyl acetate and lipase “PL-266” gave (8aR)-**65** (80% ee, 40% yield) and an acetate (8aS)-**70** (61% ee, 53% yield). Enzymatic acetylation of (±)-**67** in the presence of isopropenyl acetate and lipase “PL-266” gave (8aR)-**67** (12% ee, 46% yield) and an acetate (8aS)-**71** (12% ee, 43% yield). The results of enzymatic esterification of (±)-**64**, (±)-**65** and (±)-**67** were found to be subtly effected by the position of double bond in the substrate.

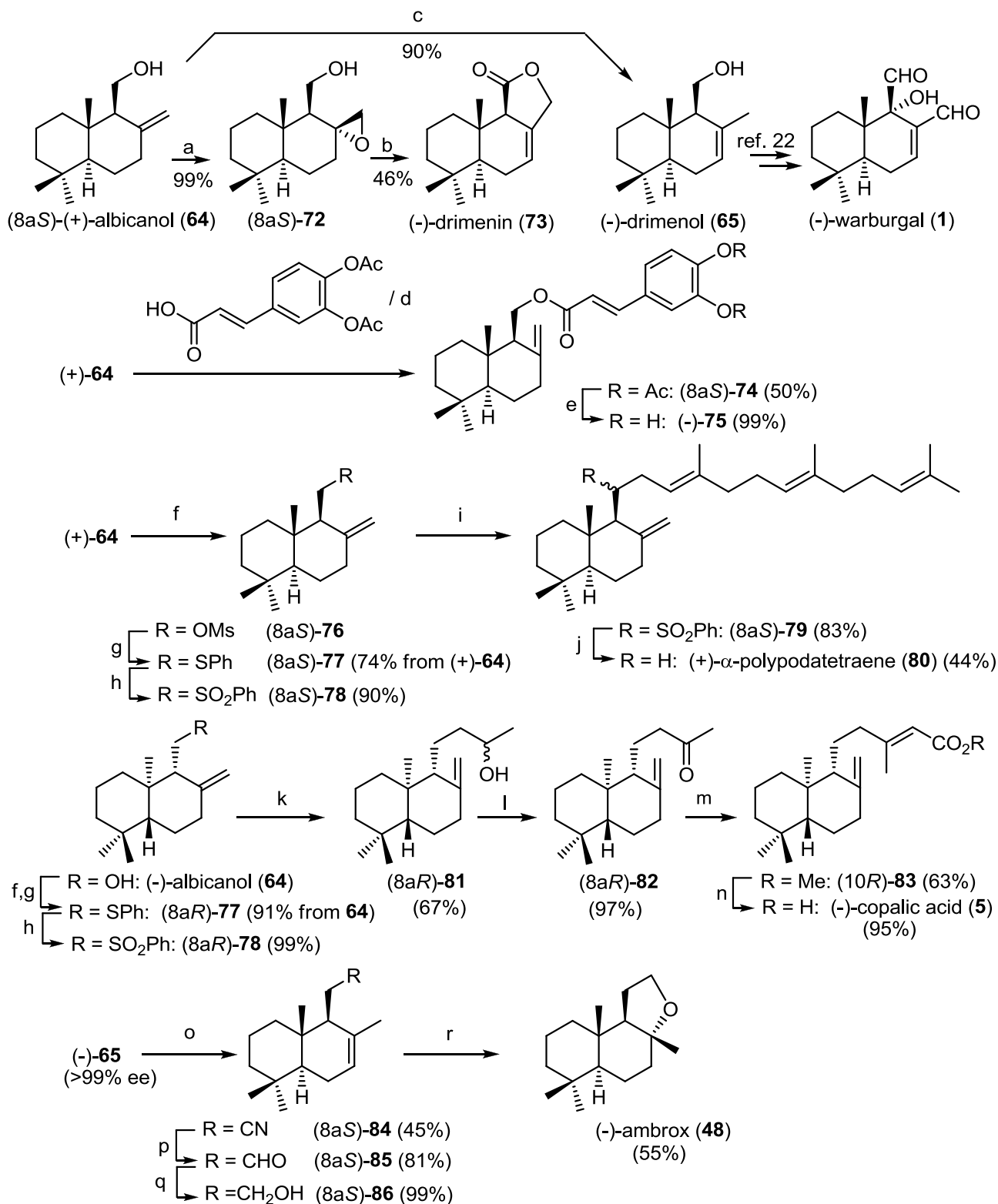


### 3.2. Syntheses of (-)-drimenin, (-)-drimenol, (-)-albicanyl 3,4-dihydroxycinnamate and formal synthesis of (-)-warburganal

(-)-Drimenin (**73**) was isolated from the stem bark of the South American *Drimys* species. Epoxidation of (+)-albicanol (**64**) gave the diastereomerically pure epoxide (8a*S*)-**72** in 99% yield. Jones oxidation of **72** followed by treatment with *p*-TsOH provided (-)-**73** in 46% overall yield from **72** as shown in Scheme 11.<sup>20</sup> (-)-Drimenol (**65**) was obtained by treatment of (+)-**64** with BF<sub>3</sub>·Et<sub>2</sub>O in 90% yield.<sup>20</sup> Acetylation of (-)-**65** gave a (8a*S*)-drimenyl acetate (**70**), which was converted to potent antifeedant such as (-)-warburganal (**1**).<sup>22</sup> (-)-Albicanyl 3,4-dihydroxycinnamate (**75**) was isolated from *Bazzania japonica* and *Bazzania pompenaa* as the major component.<sup>23</sup> The reaction of (+)-**64** and 3,4-diacetoxycinnamic acid in the presence of DCC / DMAP / CSA gave (8a*S*)-albicanyl 3,4-diacetoxycinnamate (**74**) in 50% yield, which was subjected to enzymatic hydrolysis using lipase “Amano P” to provide (-)-**75** in 99% yield.<sup>20</sup>

### 3.3. Syntheses of (+)- $\alpha$ -polypodatetraene, (-)-copalic acid and (-)-ambrox

Polypodanes constitute a new class of bicyclic terpenoids and their occurrence in nature is important for the mechanistic study of the biosynthesis of polycyclic terpenoids. (+)- $\alpha$ -Polypodatetraene (**80**) is the first compound of this class and was isolated from the fresh leaves of *Polypodium fauriei* and *Lemmaphyllum microphyllum*.<sup>24</sup> Straightforward synthesis of (+)-**80** from (+)-albicanol (**64**) was shown in Scheme 11.<sup>25</sup> Mesylation of (+)-**64** followed by treatment with benzenethiolate ion gave sulfide (8a*S*)-**77** in 74% overall yield from (+)-**64**. Oxidation of (8a*S*)-**77** with 30% H<sub>2</sub>O<sub>2</sub> in the presence of Mo<sub>7</sub>O<sub>24</sub>(NH<sub>4</sub>)<sub>6</sub>·4H<sub>2</sub>O afforded sulfone (8a*S*)-**78** in 90% yield, which was lithiated with LDA followed by treatment with (*E,E*)-farnesyl bromide to give a diastereomeric mixture of (8a*S*)-**79** in 83% yield. Treatment of (8a*S*)-**79** with 5% Na-Hg gave (+)-**80** in 44% yield. On the other hand, (-)-copalic acid (**5**) isolated from *Copaifera* sp. was reported to possess antimicrobial activity and oil resin from *Copaifera* sp. was used as traditional medicine in Brazil.<sup>26</sup> (-)-Copalic acid (**5**) could be only a natural source for the synthesis of (8a*R*)-labdane type diterpenes. Straightforward synthesis of (-)-**5** from (-)-albicanol (**64**) was shown in Scheme 11.<sup>21</sup> (8a*R*)-Albicanyl phenyl sulfone (8a*R*)-**78** was obtained from (-)-**64** in the same way as for the preparation of (8a*S*)-**78** from (+)-**64**. Treatment of (8a*R*)-**78** with *n*-BuLi followed by treatment of propylene oxide afforded the reaction product, which was subjected to reductive desulfonylation to give a diastereomeric mixture of secondary alcohol (8a*R*)-**81** in 67% overall yield. Dess-Martin oxidation of (8a*R*)-**81** provided a ketone (8a*R*)-**82** in 97% yield, which was subjected to Horner-Emmons condensation with methyl dimethoxyphosphonoacetate to afford methyl (10*R*)-(*E*)-copalate **8** in 63% yield. Alkaline hydrolysis of (10*R*)-**83** gave (-)-copalic acid (**5**) in 95% yield. Then the synthesis of (-)-ambrox (**48**) was carried out from (-)-drimenol (**65**) as shown in Scheme 11.<sup>20</sup> (-)-Ambrox (**48**) is one of the constituents of the



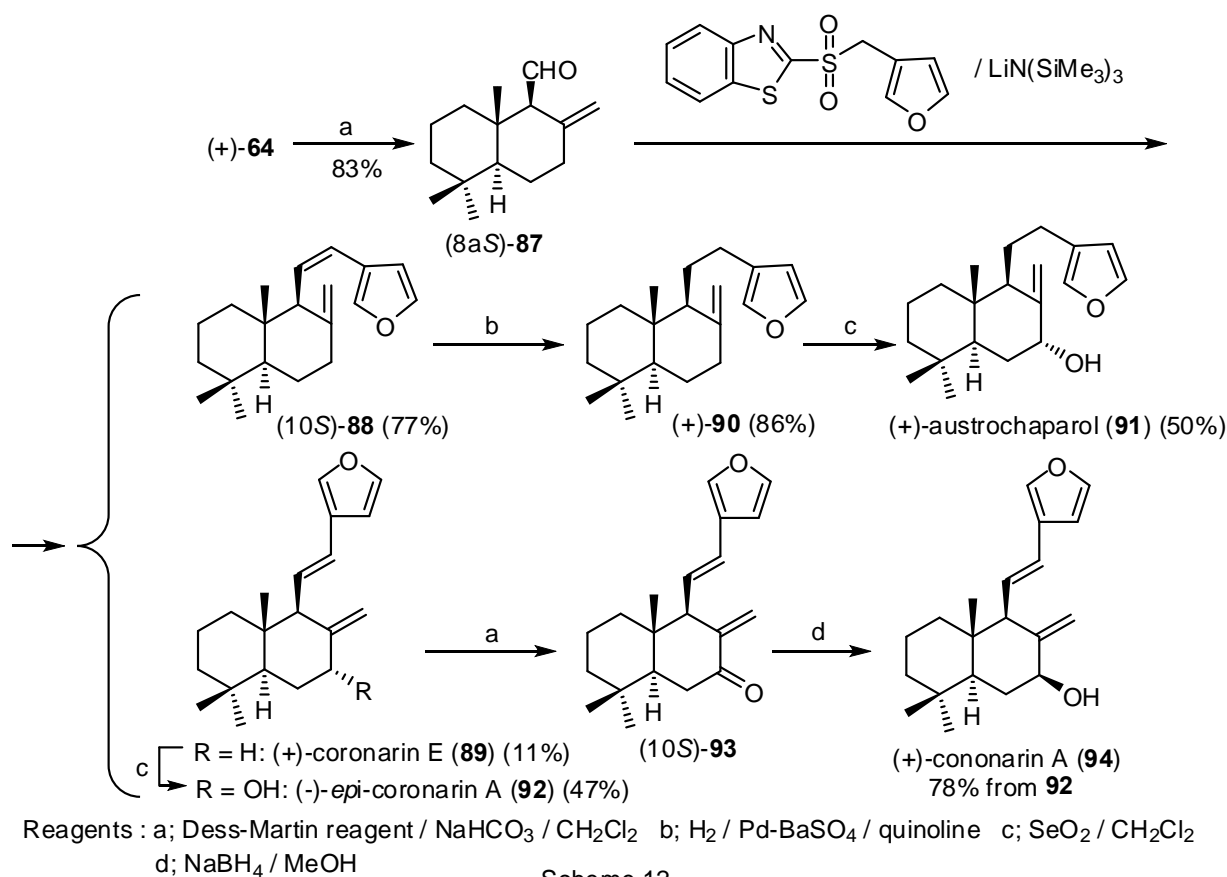
Reagents : a; *m*-CPBA b; 1) Jones reagent / acetone 2) *p*-TsOH c; BF<sub>3</sub>·Et<sub>2</sub>O d; DCC / DMAP / CSA  
 e; lipase "Amano P" f; MsCl / 4-DMAP / pyridine g; PhSH / NaH / DMSO  
 h; 30% H<sub>2</sub>O<sub>2</sub> / Mo<sub>7</sub>O<sub>24</sub>(NH<sub>4</sub>)<sub>6</sub>·4H<sub>2</sub>O / EtOH i; 1) *i*-Pr<sub>2</sub>NLi (LDA) / THF 2) (*E,E*)-farnesyl bromide  
 j; 5% Na-Hg / MeOH k; 1) *n*-BuLi / propylene oxide 2) Na / Na<sub>2</sub>HPO<sub>4</sub> / EtOH / THF  
 l; Dess-Martin periodinane / CH<sub>2</sub>Cl<sub>2</sub> m; (MeO)<sub>2</sub>P(=O)CH<sub>2</sub>CO<sub>2</sub>Me / NaH / DMF  
 n; 1) 2M NaOH / EtOH 2) 2M HCl o; 1) MsCl / pyridine 2) NaCN / DMSO  
 p; 1) Dibal-H 2) H<sup>+</sup> q; NaBH<sub>4</sub> r; *p*-TsOH / MeCN

Scheme 11

*ambergris* tincture and possesses a powerful amber-type aroma. Mesylation of (-)-**65** followed by treatment with NaCN gave nitrile compound (8a*S*)-**84** in 45% overall yield, which was reduced with Dibal-H to afford an aldehyde (8a*S*)-**85** in 81% yield. NaBH<sub>4</sub> reduction of (8a*S*)-**85** provided an alcohol (8a*S*)-**86**, which was treated with *p*-TsOH to give (-)-ambrox (**48**) in 55% yield.

### 3.4. Syntheses of (+)-austrochaparol, (+)-coronarin A and (+)-coronarin E

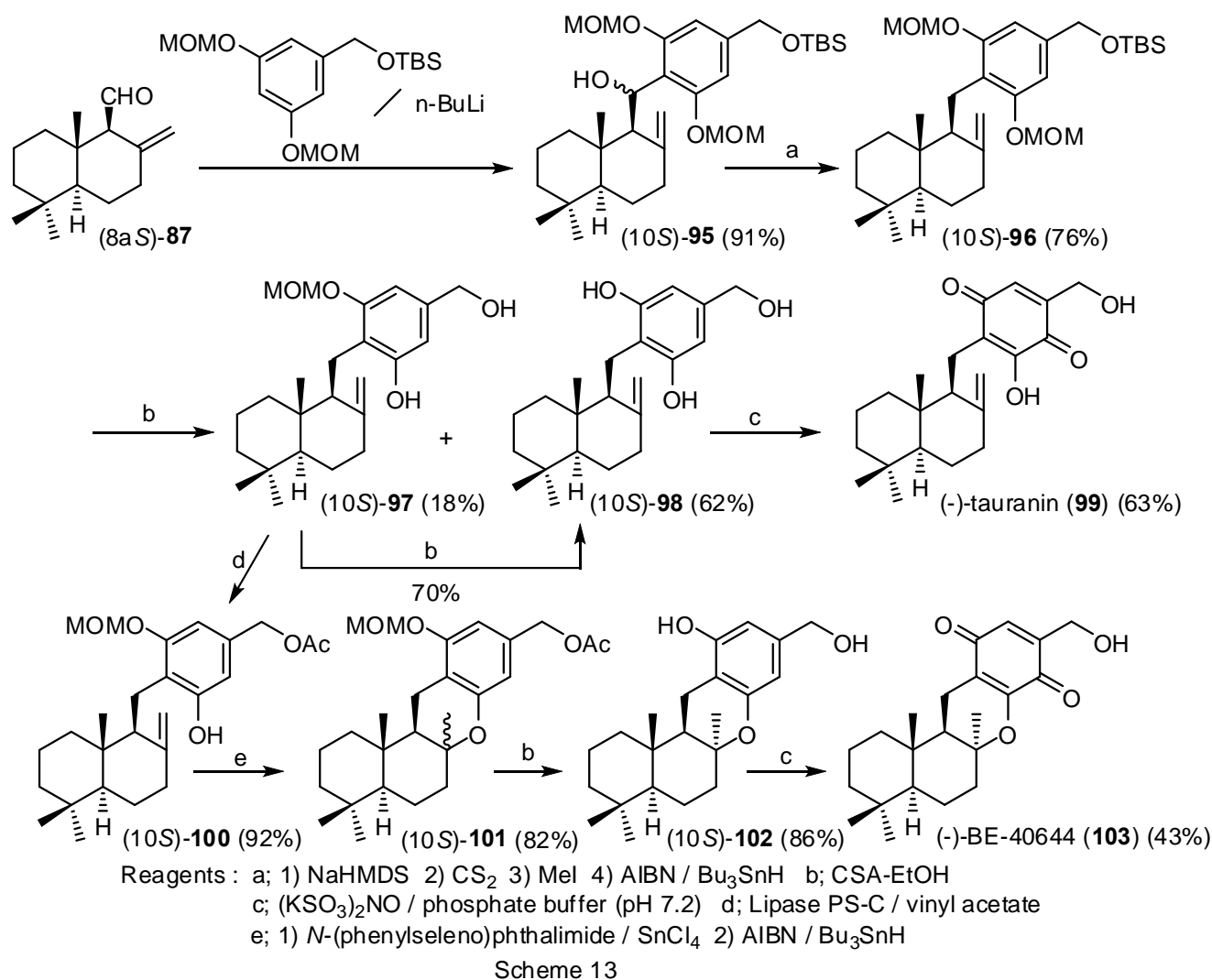
(+)-Austrochaparol (**91**) was isolated from the aerial parts of *Austro eupatorium chaparensis* and its absolute structure has not been determined yet.<sup>27</sup> (+)-Coronarin A (**94**) and (+)-coronarin E (**89**) were isolated from rhizomers of the Brazilian antirheumatic medical plant, *Hedychium coronarium*.<sup>28</sup> These compounds exhibit a significant cytotoxic effect against Chinese hamster V-79 cells and sarcoma 180 ascites in mice. For the synthesis of these compounds, carbon-carbon bond formation between an aldehyde (8a*S*)-**87** and β-furylmethyl heteroaromatic sulfone is necessary as shown in Scheme 12.<sup>29</sup> The reaction of 3-furylmethanol with 2-mercaptobenzothiazole (BTSH) in the presence of Ph<sub>3</sub>P and diethyl azodicarboxylate (DEAD) gave sulfide, which was oxidized with *m*-CPBA to afford β-furylmethyl benzothiazoly sulfone. Dess-Martin oxidation of (+)-albicanol (**64**) gave an aldehyde (8a*S*)-**87** in 83% yield, which was reacted with the above mentioned sulfone in the presence of lithium bis(trimethylsilylamide) to afford (10*S*)-**88** (77%) and (+)-coronarin E (**89**) (11% yield). Hydrogenation



of (10*S*)-**88** gave compound (+)-**90** in 86% yield, which was in accord with the natural product (+)-(5*S*,9*S*,10*S*)-15,16-epoxy-8(17),13(16),14-labdatriene. Allylic oxidation of (+)-**90** with SeO<sub>2</sub> gave (+)-austrochaparol (**91**) in 50% yield. Consequently, absolute configurations of natural (+)-austrochaparol (**91**) were confirmed to be 5*S*, 7*R*, 9*R*, 10*S*. On the other hand, allylic oxidation of (+)-**89** with SeO<sub>2</sub> afforded (-)-**92** in 47% yield, which was subjected to Dess-Martin oxidation to provide  $\alpha,\beta$ -unsaturated a ketone (10*S*)-**93**. NaBH<sub>4</sub> reduction of (8*aS*)-**93** gave (+)-coronararin A (**94**) in 78% overall yield from (-)-**92**.

### 3.5. Syntheses of (-)-tauranin and (-)-BE-40644

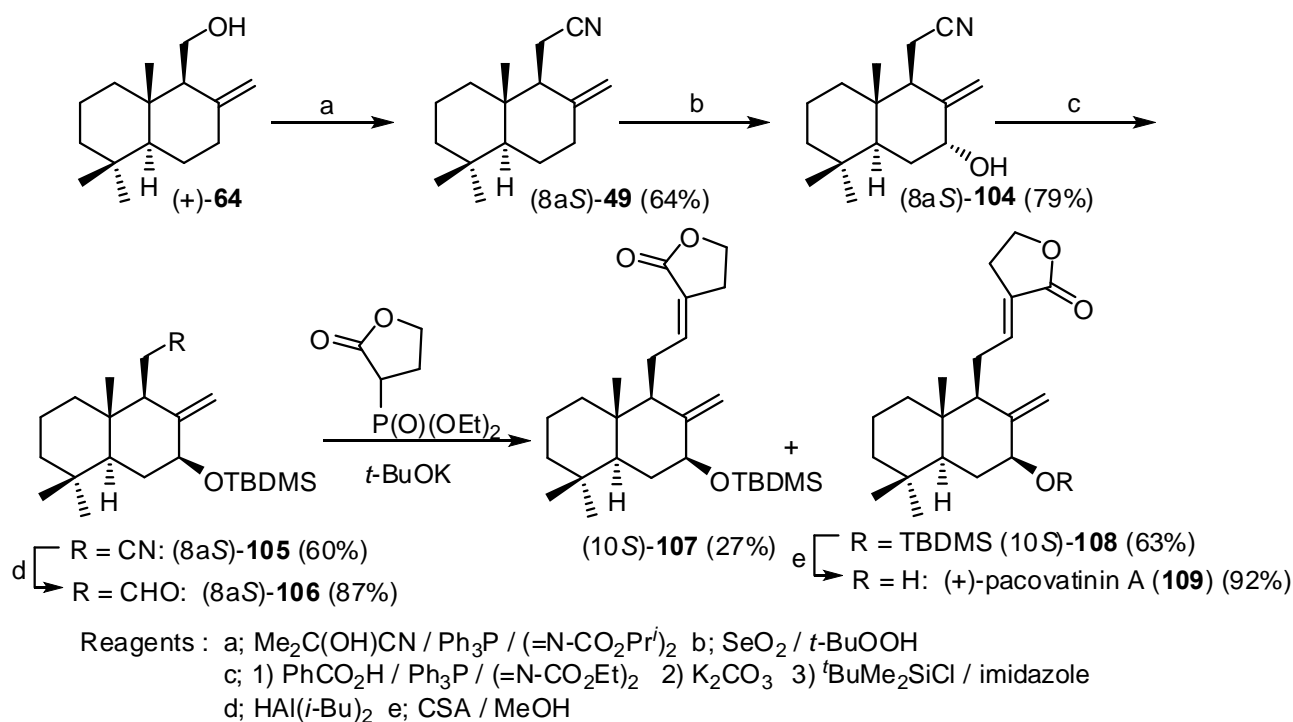
A sesquiterpene quinone (-)-tauranin (**99**) was isolated from mold *Oospora aurantia* and fungus *Phyllosticta spinarum*.<sup>30</sup> It has been reported to possess apoptotic activity toward several human solid tumor cell lines,<sup>31</sup> and inhibitory activity against the incorporation of acetate-1-<sup>14</sup>C into cholesterol.<sup>32</sup> Meanwhile, sesquiterpene quinone (-)-BE-40644 (**103**) was isolated from *Actinoplanes* sp. A 40644<sup>33</sup> and reported to inhibit the thioredoxin (TRX) system and to exhibit cytotoxicity against several human tumor cell lines. In addition, strong repression of human immunodeficiency virus (HIV) replication was also reported for this compound.<sup>34</sup> In spite of its interesting biological activities, the absolute configurations of (-)-**103** have not been determined. The synthesis of (-)-**99** and (-)-**103** was shown in Scheme 13.<sup>35</sup> Common aromatic building block, 4-[(*t*-butyldimethylsilyl)oxymethyl]-2,6-di(methoxymethoxy)-benzene for the syntheses of (-)-**99** and (-)-**103** was prepared from methyl 3,5-dihydroxybenzoate. The previous aldehyde (8*aS*)-**87** was reacted with an anion generated from the above mentioned building block by treatment with *n*-BuLi to afford a diastereomeric mixture of (10*S*)-**95** in 91% yield, which was subjected to Barton McCombie's method<sup>36</sup> to afford (10*S*)-**96** in 76% overall yield. For preparation of (10*S*)-**98**, (10*S*)-**96** was treated with 100 mM of CSA in EtOH for 3.5 days to afford (10*S*)-**97** (18% yield) and (10*S*)-**98** (62% yield). Furthermore, (10*S*)-**97** was again treated with 100 mM of CSA in EtOH to give (10*S*)-**98** in 70% yield. Oxidation of (10*S*)-**98** by Fremy's salt [(KSO<sub>3</sub>)<sub>2</sub>NO] in phosphate buffer gave (-)-tauranin (**99**) in 63% yield. On the other hand, regioselective acetylation of (10*S*)-**97** with vinyl acetate catalyzed by lipase PS-C to afford (10*S*)-**100** in 92% yield. Treatment of (10*S*)-**100** with *N*-(phenylseleno)phthalimide afforded a diastereomeric mixture of phenylselenide derivatives, whose phenylselenyl group was removed by tributyltinhydride in the presence of AIBN to afford (10*S*)-**101** as a diastereomeric mixture (6*aS* : 6*aR* = 11:1) in 82% overall yield. Treatment of (10*S*)-**101** with CSA followed by silicagel column chromatographic separation afforded (10*S*)-**102** as a single isomer in 86% yield. It was treated with Fremy's salt in phosphate buffer to give (-)-BE-40644 (**103**) in 43% yield. Synthetic (-)-BE-40644 (**103**) was identical with natural (-)-BE-40644 (**103**) and the absolute structure of natural (-)-**103** was determined to be 4*aS*, 6*aS*, 12*aR*, 12*bS*.



### 3.6. Synthesis of (+)-pacovatinin A

(+)-Pacovatinin A (**109**) was isolated from seeds of the Brazilian medicinal plant, *Renalmia exaltata* L.f. (Zingiberaceae)<sup>37</sup> and found to inhibit the increase of vascular permeability induced by acetic acid in mice and nitric oxide production in lipopolysaccharide-activated mouse peritoneal macrophages.<sup>38</sup> The straightforward synthesis of (+)-**109** from (+)-albicanol (**64**) is shown in Scheme 14.<sup>29</sup> Conversion of (+)-**64** to albicanyl cyanide (8a*S*)-**49** was accomplished by displacement of the hydroxyl group with cyanide under Mitsunobu conditions<sup>39</sup> in the presence of acetone cyanohydrin to give nitrile (8a*S*)-**49** in 64% yield. Allylic oxidation of (8a*S*)-**49** using a combination of SeO<sub>2</sub> and *tert*-BuOOH gave the 7α-hydroxy compound (8a*S*)-**104** in 79% yield. Stereochemical inversion of 7α-configuration to 7β-configuration was achieved by the Mitsunobu method.<sup>39</sup> Treatment of (8a*S*)-**104** with PhCO<sub>2</sub>H in the presence of Ph<sub>3</sub>P and diethyl azodicarboxylate afforded 7β-acyloxy nitrile, which was successively treated with K<sub>2</sub>CO<sub>3</sub> in MeOH and <sup>t</sup>BuMe<sub>2</sub>SiCl in the presence of imidazole to afford (8a*S*)-**105** in 60% yield. Dibal-H reduction of (8a*S*)-**105** gave an aldehyde (8a*S*)-**106** in 87% yield, which was subjected to

Horner-Emmons condensation with diethoxyphosphonobutyrolactone in the presence of *tert*-BuOK to provide the less polar compound (10*S*)-**107** (27% yield) and the more polar one (10*S*)-**108** (63% yield). Deprotection of silyl group of (10*S*)-**108** provided (+)-pacovatinin A (**109**) in 92% yield.

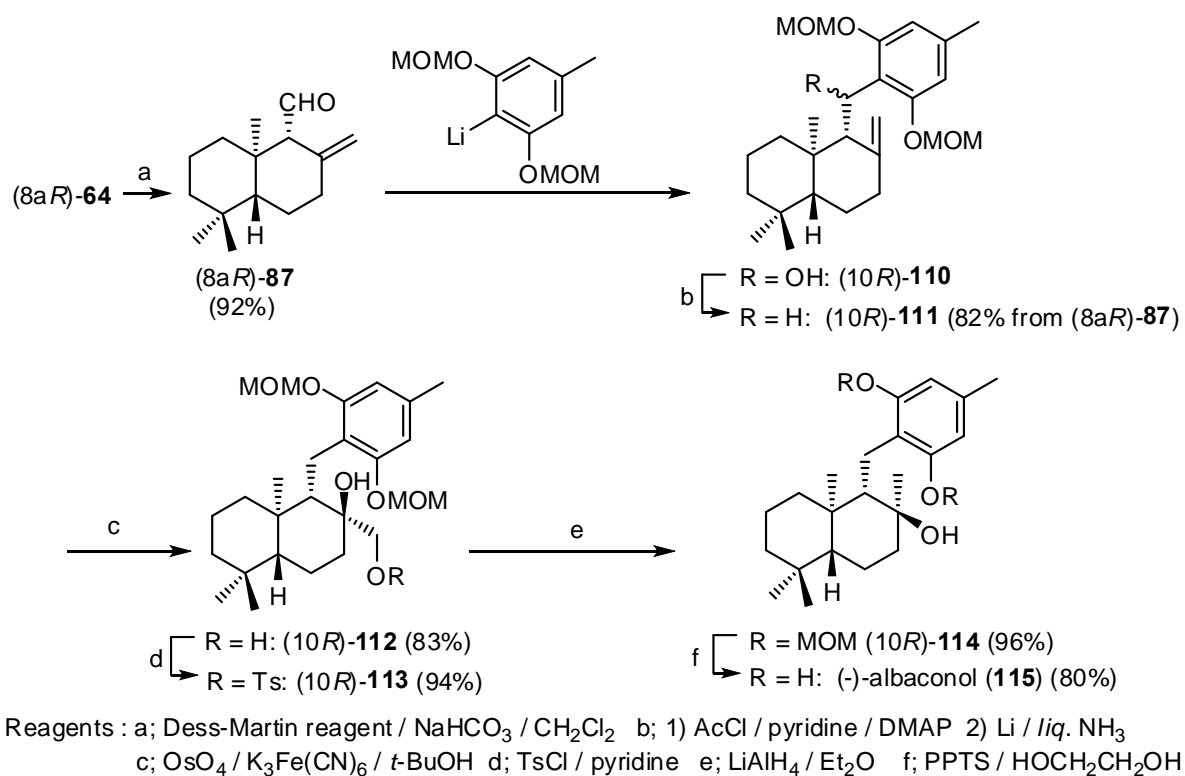


Scheme 14

### 3.7. Synthesis of (-)-albaconol

Albaconol (**115**) was isolated from the fresh fruiting bodies of the basidiomycetes *Albatrellus confluentis*,<sup>40</sup> and acts as weak antagonists for human vanilloid-receptor (VRI) without agonistic effect.<sup>41</sup> Albaconol (**115**) inhibits significantly the growth of human tumor cell lines *in vitro*, and stimulates DNA cleavage, stabilizes and increases the topo II-mediated DNA cleavable complex because of inhibition the religation activity of topo II in a dose-dependent manner.<sup>42</sup> Structure of **115** was determined by spectral analysis but the absolute structure of **115** was not determined yet. We report the first synthesis of (8*aR*)-albaconol (**115**) from (8*aR*)-albicanol (**64**) and determination of the absolute structure of natural albaconol (**115**) based on chiral synthesis (8*aR*)-**115** as shown in Scheme 15.<sup>43</sup> Dess-Martin oxidation of (8*aR*)-**64** gave a (8*aR*)-albicanal (**87**) in 92% yield, which was treated with 3,5-bis-(methoxymethoxy)toluene in the presence of *n*-BuLi to afford a diastereomeric mixture of (10*R*)-**110**. Acetylation of (10*R*)-**110** followed by the Birch reduction provided (10*R*)-**111** in 82% overall yield from (8*aR*)-**87**. Dihydroxylation of the *exo*-olefin part of (10*R*)-**111** using OsO<sub>4</sub>/K<sub>3</sub>Fe(CN)<sub>6</sub> gave stereoselectively the desired diol (10*R*)-**112** in 83% yield, which is corresponding to the dihydroxylation

product from less-hindered  $\beta$ -side. The relative configuration of C(2)-position in (10*R*)-**112** could be *S*, because the present (10*R*)-**112** was finally converted to the enantiomer of natural albaconol (10*S*)-**115** as mentioned later on. Monotosylation of (10*R*)-**112** gave selectively primary tosylate (10*R*)-**113** in 94% yield, which was treated with LiAlH<sub>4</sub> to afford tertiary alcohol (10*R*)-**114** in 96% yield. Finally, (10*R*)-**114** was treated with pyridinium *p*-toluenesulfonate (PPTS) in the presence of ethylene glycol to afford (10*R*)-(-)-albaconol (**115**) in 80% yield. In this case, PPTS was used as weak acid to avoid formation of ether linkage between phenolic hydroxyl group and C(2)-carbon. The physical data of the synthetic (10*R*)-**115** were identical with those of natural albaconol (**115**) except for the sign of the specific rotation. From these evidences, the absolute structure of natural (+)-albaconol (**115**) was determined to be 1*R*,2*R*,4*aS*,8*aS* configurations.



Scheme 15

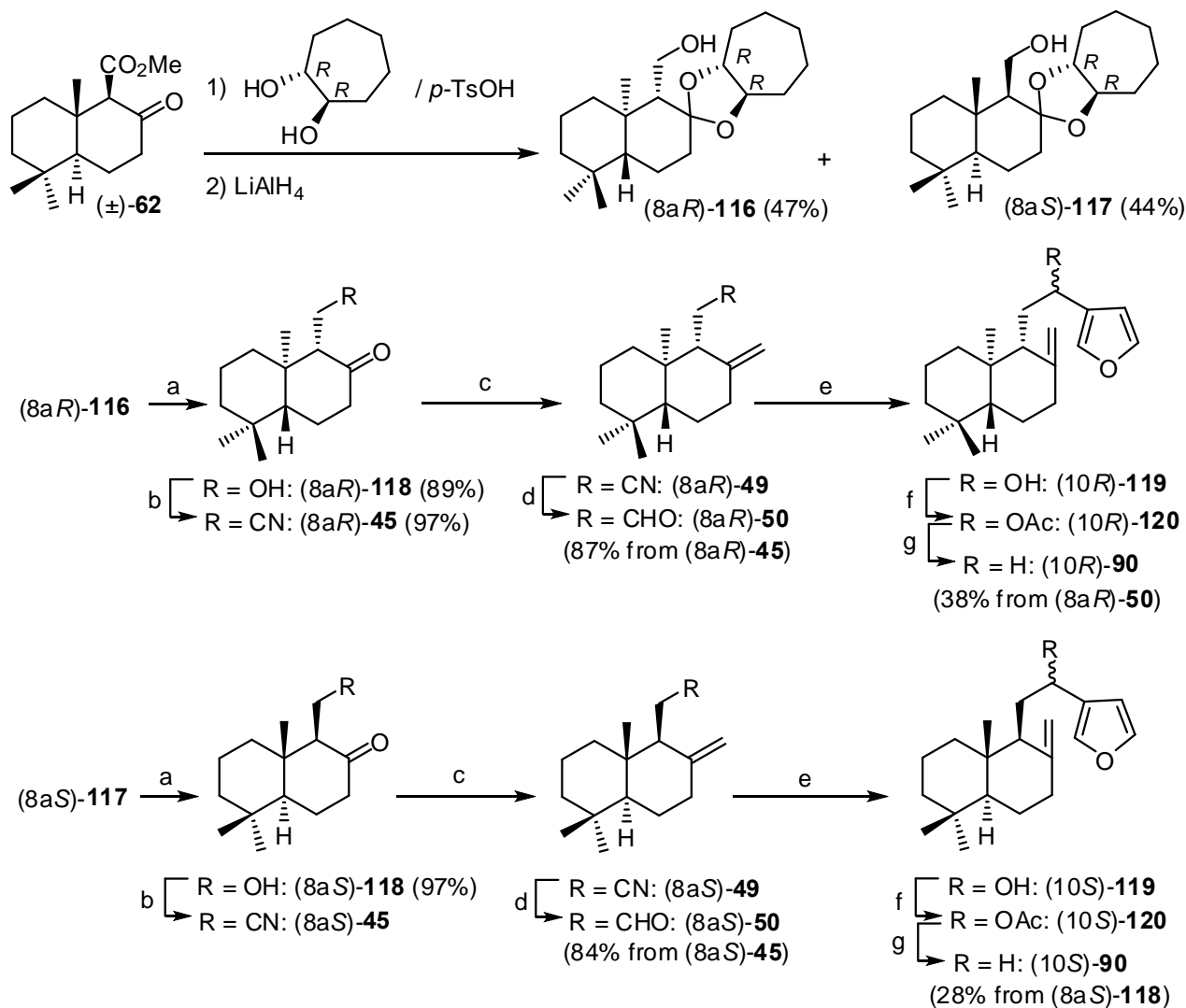
#### 4. SYNTHESIS OF BOTH ENANTIOMERS OF VERSATILE CHIRAL SYNTHON BASED ON OPTICAL RESOLUTION USING (*R,R*)-CYCLOHEPTANE 1,2-DIOL AND THEIR APPLICATION TO THE SYNTHESIS OF FURANODITERPENE

##### 4.1. Synthesis of (*8aR*)- and (*8aS*)-decahydro-5,5,8*a*-trimethyl-2-oxo-naphthalene-1-methanol

Chiral auxiliary, (*R,R*)-cycloheptane 1,2-diol was obtained based on enzymatic hydrolysis of *meso*-1,2-cycloheptane diacetate.<sup>44</sup> The reaction of ( $\pm$ )- $\beta$ -keto ester (**62**) and (*R,R*)-cycloheptane 1,2-diol in the presence of *p*-TsOH followed by LiAlH<sub>4</sub> reduction gave a diastereomeric mixture of alcohols **116**

and **117**, which were separated by silicagel chromatography to give the less polar alcohol **116** in 47% overall yield from ( $\pm$ )-**62** and the more polar alcohol **117** in 44% overall yield from ( $\pm$ )-**62**. Acid treatment of **116** gave the (+)-hydroxy ketone (**118**) (89% yield) and (*R,R*)-cycloheptane 1,2-diol (87% yield). The physical data of (+)-**118** was identical to those of the previously reported (+)-(8*aR*)-**118**<sup>45</sup>. On the other hand, acid treatment of **117** gave the (-)-hydroxy ketone (**118**) (97% yield) and (*R,R*)-cycloheptane 1,2-diol (97% yield). The physical data of (-)-**118** was identical to those of the previously reported (-)-(8*aS*)-**118**<sup>45</sup> and the absolute configuration of the present **117** was determined to 1*S*,4*aS*,8*aS* as shown in Scheme 16.<sup>46</sup> The present resolution procedure seemed to be highly advantageous because the (*R,R*)-cycloheptane 1,2-diol could be recovered in high yield from the chiral acetals **116** and **117** by treatment with acid and could then be again used for chiral acetal formation.

#### 4.2. Synthesis of both (10*R*)- and (10*S*)-15,16-epoxy-8(17)13(16)-labdatrienes



Reagents : a; 10% HCl aq. b; 1)  $\text{Ac}_2\text{O}$  / pyridine 2)  $\text{NaCN}$  / DMF c;  $\text{Ph}_3\text{P}^+\text{Me Br}^-$  /  $\text{NaNH}_2$  / toluene

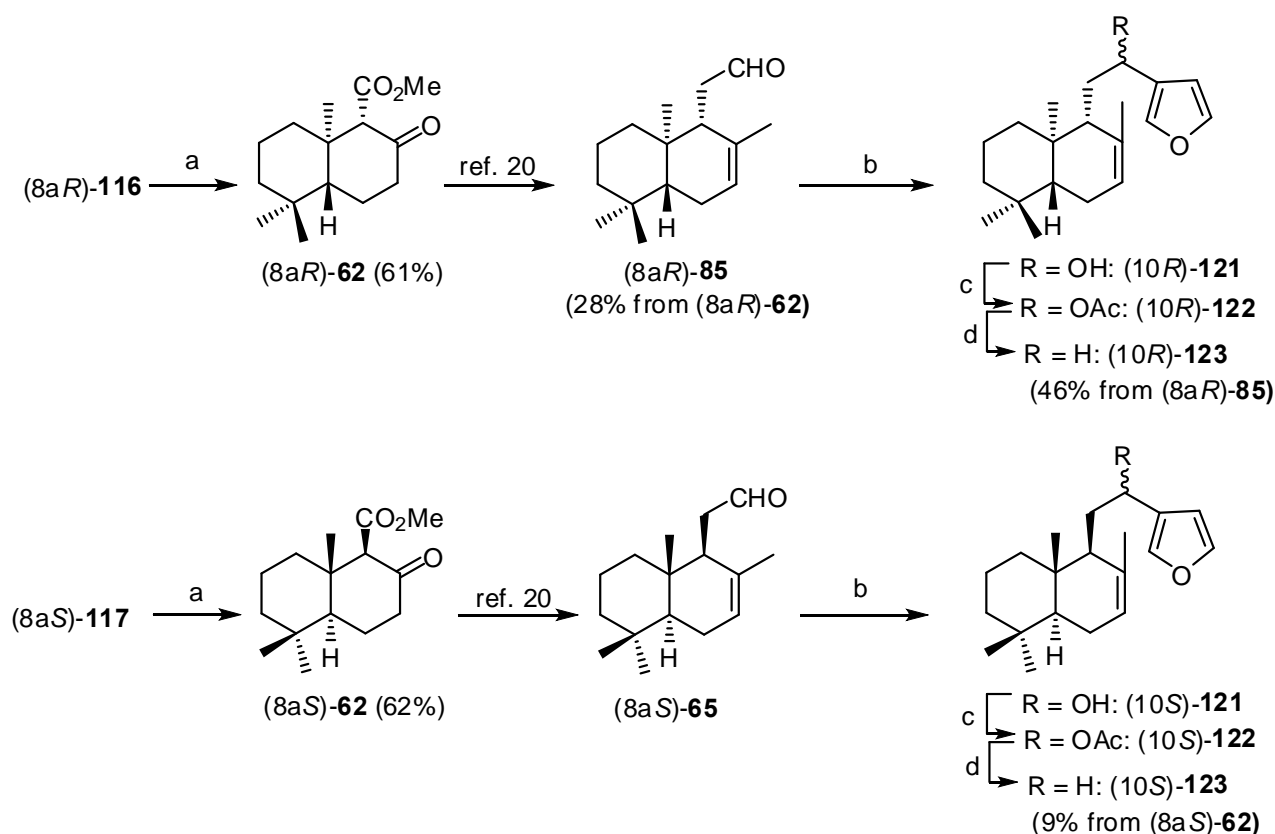
d;  $\text{HAl}(i\text{-Bu})_2$  / toluene e; 3-bromofuran / *n*-BuLi / THF f;  $\text{Ac}_2\text{O}$  / pyridine g; Li / liq.  $\text{NH}_3$  / THF

Scheme 16

(-)-15,16-Epoxy-8(17)13(16)-labdatriene (**90**) has been isolated from the Philippine sponge, *Cacospongia* species.<sup>47</sup> The *ent*-type of **90** has been isolated from the aerial part of *Blepharispermum zanguebaricum*. However, the absolute structure of two (+)- and (-)-furanoditerpenes **90** has not been determined yet. The syntheses of (10*R*)-**90** from (+)-(8*aR*)-**118** and (10*S*)-**90** from (-)-(8*aS*)-**118** were shown in Scheme 16.<sup>46</sup> Acetylation of (8*aR*)-**118** followed by treatment with NaCN gave a  $\gamma$ -keto nitrile (8*aR*)-**45** in 97% overall yield from (8*aR*)-**118**, of which the physical data were identical with those of the reported (8*aS*)-**45**<sup>14</sup> except for the sign of specific rotation. Wittig olefination of (8*aR*)-**45** followed by reduction with Dibal-H yielded the corresponding aldehyde (8*aR*)-**50** in 87% overall yield from (8*aR*)-**45**. The spectral data of (8*aR*)-**50** were identical with those of the reported (8*aR*)-**50**.<sup>17</sup> Aldehyde (8*aR*)-**50** was reacted with 3-lithiofuran to afford a diastereomeric mixture of secondary alcohol (10*R*)-**119**, which was subjected to acetylation followed by a Birch reduction to give a furanoditerpene (10*R*)-**90** ( $[\alpha]_D -42.6$  (CHCl<sub>3</sub>)) in 38% overall yield from (8*aR*)-**50**. Similarly, antipodal furanoditerpene (10*S*)-**90** ( $[\alpha]_D +49.3$  (CHCl<sub>3</sub>)) was also synthesized from (8*aS*)-**118** in 28% overall yield from (8*aS*)-**118** in the same way as for (8*aR*)-**90**. The NMR data of both enantiomers (10*R*)- and (10*S*)-**90** were identical with those of the natural (-)-**90** and the sign of (10*R*)-**90** was the same as that of the natural (-)-**90**. Hence, the absolute structure of the natural (-)-**90** was unequivocally determined as (5*R*,9*R*,10*R*) as depicted in Scheme 16.

#### 4.3. Synthesis of both (10*R*)- and (10*S*)-15,16-epoxy-7,13(16),14-labdatrienes

(+)-15,16-Epoxy-7,13(16),14-labdatriene (**123**) has been isolated from the Philippine sponge, *Cacospongia* sp.<sup>48</sup> However, the absolute structure of two (+)-furanoditerpene **123** has not been determined yet. The syntheses of (10*R*)-**123** from (+)-(8*aR*)-**116** and (10*S*)-**123** from (-)-(8*aS*)-**117** were shown in Scheme 17.<sup>46</sup> Oxidation of (8*aR*)-**116** with PCC gave an aldehyde, which was subjected to oxidation with NaClO<sub>2</sub> followed by esterification to afford methyl ester. The methyl ester was treated with 10% aqueous H<sub>2</sub>SO<sub>4</sub> to provide the (8*aR*)- $\beta$ -keto ester (**62**) in 61% overall yield. Conversion of (8*aR*)-**62** to aldehyde (8*aR*)-**85** was achieved by our previously reported procedure (Scheme 11).<sup>20</sup> The reaction of (8*aR*)-**85** with 3-lithiofuran prepared from 3-bromofuran and *n*-BuLi furnished a diastereomeric mixture of secondary alcohol (10*R*)-**121**, which was subjected to acetylation followed by a Birch reduction to give a furanoditerpene (10*R*)-**123** ( $[\alpha]_D -14.2$  (CHCl<sub>3</sub>)) in 46% overall yield from (8*aR*)-**85**. Similarly, antipodal furanoditerpene (10*S*)-**123** ( $[\alpha]_D +11.6$  (CHCl<sub>3</sub>)) was also synthesized from (8*aS*)-**117** in the same way as for (8*aR*)-**123**. The NMR data of both enantiomers (10*R*)- and (10*S*)-**123** were identical with those of the natural (+)-**123** and the sign of (10*S*)-**123** was the same as that of the natural (+)-**123** ( $[\alpha]_D +3.2$  (CHCl<sub>3</sub>)). Hence, the absolute structure of the natural (+)-**123** was unequivocally determined as (5*S*,9*S*,10*S*) as depicted in Scheme 17.



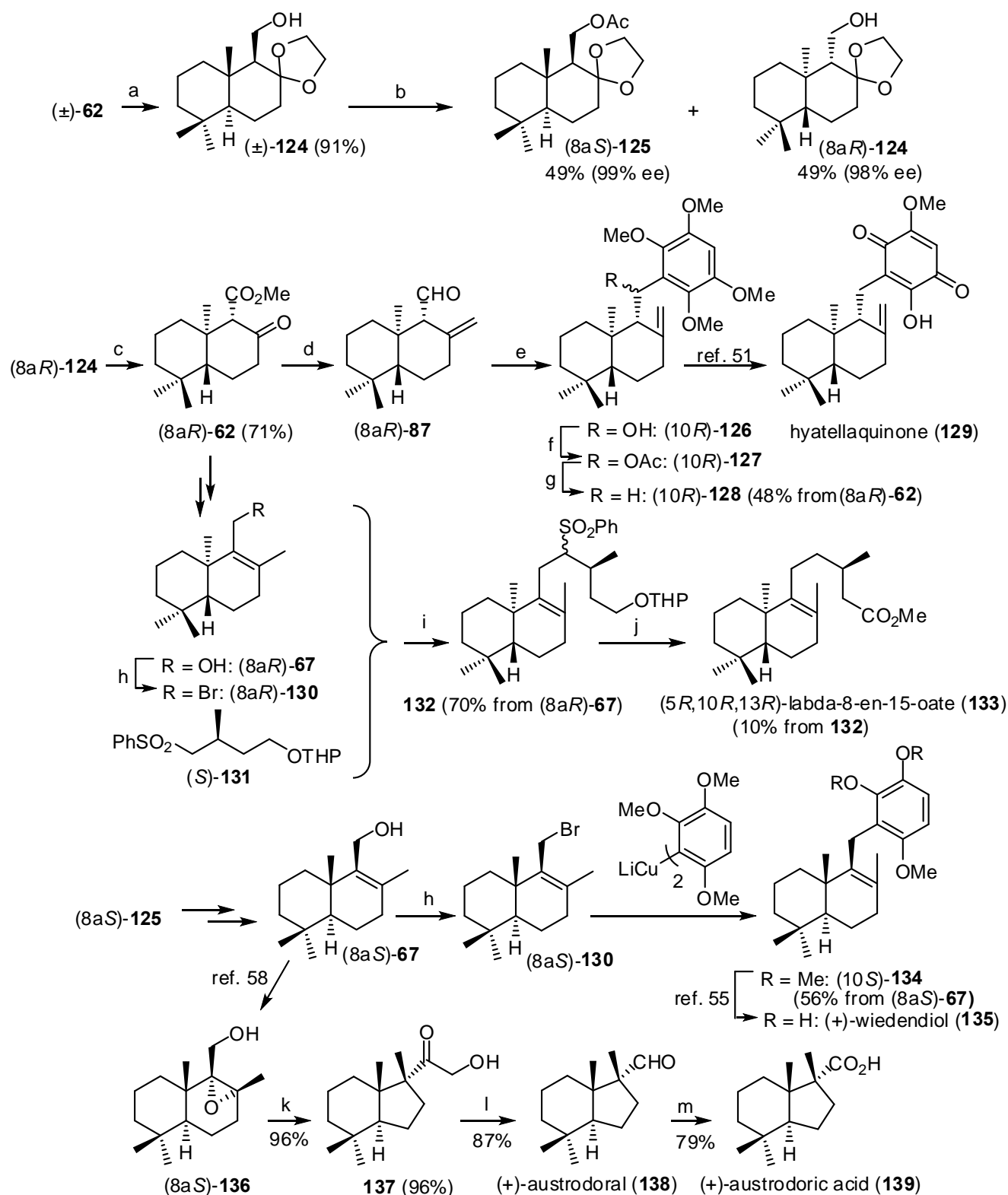
Reagents : a; 1) PCC / CH<sub>2</sub>Cl<sub>2</sub> 2) NaClO<sub>2</sub> / NaH<sub>2</sub>PO<sub>4</sub> / 2-methyl-2-butene / *t*-BuOH 3) CH<sub>2</sub>N<sub>2</sub>  
 4) 10% H<sub>2</sub>SO<sub>4</sub> aq. / MeOH b; 3-bromofuran / *n*-BuLi / THF c; Ac<sub>2</sub>O / pyridine  
 d; Li / liq. NH<sub>3</sub> / THF

Scheme 17

## 5. SYNTHESIS OF BOTH ENANTIOMERS OF VERSATILE CHIRAL SYNTHON BASED ON ENZYMATIC RESOLUTION AND THEIR APPLICATION TO THE SYNTHESIS OF THE RELATED NATURAL PRODUCTS

### 5.1. Synthesis of (8aR)- and (8aS)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol-2-ethylene acetal

The substrate, (±)-decahydro-5,5,8a-trimethyl-2-oxo-naphthalene-1-methanol-2-ethylene acetal (**124**) for enzymatic reaction was synthesized from (±)-β-keto ester (**62**) as shown in Scheme 18.<sup>49</sup> The reaction of (±)-**62** and ethylene glycol in the presence of *p*-TsOH gave the corresponding acetal, which was reduced with LiAlH<sub>4</sub> to afford (±)-**124** in 91% overall yield from (±)-**62**. From a screening experiment using various kinds of lipases, lipase “PL-266” from *Alcaligenes* sp. was found to be effective lipase. A suspension of (±)-**124**, isopropenyl acetate and lipase “PL-266” in diisopropyl ether was incubated at



Reagents : a; 1) ethylene glycol / *p*-TsOH 2) LiAlH<sub>4</sub> b; lipase "PL-266" / isopropenyl acetate / (*i*-Pr)<sub>2</sub>O  
 c; 1) PCC / CH<sub>2</sub>Cl<sub>2</sub> 2) NaClO<sub>2</sub> / NaH<sub>2</sub>PO<sub>4</sub> / 2-methyl-2-butene / *t*-BuOH 3) CH<sub>2</sub>N<sub>2</sub>  
 4) 10% HCl aq. / MeOH d; 1) Ph<sub>3</sub>P<sup>+</sup>Me Br<sup>-</sup> / NaNH<sub>2</sub> / toluene 2) LiAlH<sub>4</sub> 3) PCC / CH<sub>2</sub>Cl<sub>2</sub>  
 e; 1,2,4,5-tetramethoxybenzene / *n*-BuLi / THF f; Ac<sub>2</sub>O / DMAP / pyridine  
 g; Li / *liq.* NH<sub>3</sub> / THF h; PBr<sub>3</sub> / pyridine / Et<sub>2</sub>O i; LDA / HMPA / THF  
 j; 1) 5% Na-Hg / Na<sub>2</sub>HPO<sub>4</sub> / MeOH 2) PPTS / MeOH 3) CrO<sub>3</sub> / H<sup>+</sup> / acetone 4) CH<sub>2</sub>N<sub>2</sub>  
 k; CF<sub>3</sub>CO<sub>2</sub>H l; 1) NaBH<sub>4</sub> / MeOH 2) NaIO<sub>4</sub> / *t*-BuOH / H<sub>2</sub>O m; CrO<sub>3</sub> / H<sup>+</sup> / acetone

Scheme 18

33 °C for 1 day and an acetate (8a*S*)-**125** (49%, 99% ee) and unchanged (8a*R*)-**124** (49%, 98% ee) were obtained. Oxidation of (8a*R*)-**124** with PCC gave an aldehyde, which was subjected to oxidation with NaClO<sub>2</sub> followed by esterification to afford methyl ester. The methyl ester was treated with 10% aqueous HCl to provide the (8a*R*)-β-keto ester (**62**) in 71% overall yield. The present (8a*R*)-**62** was identical with the previously mentioned (8a*R*)-**62** as shown in Scheme 17.

## 5.2. Formal synthesis of hyatellaquinone

Hyatellaquinone (**129**) was reported to inhibit the reverse transcriptase of human immunodeficiency virus (HIV)<sup>50</sup> and was formally synthesized from (8a*R*)-**62** as shown in Scheme 18.<sup>49</sup> Wittig olefination of (8a*R*)-**62** followed by consecutive reduction and oxidation gave an aldehyde (8a*R*)-**87**. The reaction of (8a*R*)-**87** with an anion prepared from 1,2,4,5-tetramethoxybenzene and *n*-BuLi furnished a diastereomeric mixture of secondary alcohol (10*R*)-**126**, which was subjected to acetylation followed by a Birch reduction to give (10*R*)-**128** in 48% overall yield from (8a*R*)-**62**. Conversion of (10*R*)-**128** to hyatellaquinone (**129**) was already achieved.<sup>51</sup>

## 5.3. Synthesis of methyl (5*R*,10*R*,13*R*)-labda-8-en-15-oate

Marine dorid nudibranchs are known to contain terpenoid glyceryl esters in their mantle. Among them, a single specimen of the Antarctic nudibranch *Austrodoris kerguelensis* contained two major glyceride ester, 2'-acetoxyglyceryl- and 3'-acetoxyglyceryl-(5*R*,10*R*,13*R*)-labda-8-en-15-oate.<sup>52</sup> These terpenoid glyceryl ester are potent activators of protein kinase C and very active in a regenerative test with the fresh water hydrozoan *Hydra vulgaris*. We tried to synthesize methyl (5*R*,10*R*,13*R*)-labda-8-en-15-oate (**133**) corresponding to the left carboxylic acid part of the above mentioned terpenoid glyceryl ester as shown in Scheme 18.<sup>25</sup> Target molecule (**133**) could be obtained by coupling reaction of (8a*R*)-bicyclofarnesyl bromide (**130**) and chiral isoprene unit (*S*)-**131**.<sup>25</sup> (8a*R*)-Bicyclofarnesol (**67**) was obtained from (8a*R*)-**62** by the same way as the preparation of (±)-**67** from (±)-**62** as shown in Scheme 9 and was treated with PBr<sub>3</sub> to give (8a*R*)-**130**. Treatment of (*S*)-**131** with lithium diisopropylamide (LDA) gave the corresponding anion, which was subjected to the coupling reaction with (8a*R*)-**130** to afford the coupling product (**132**) in 70% overall yield from (8a*R*)-**67**. Reduction of **132** with Na/Hg in MeOH followed by deprotection of THP group provided an alcohol, which was subjected to the consecutive oxidation and esterification to afford the final compound (**133**) in 10% overall yield from **132**.

## 5.4. Formal synthesis of (+)-wiedendiol

(+)-Wiedendiol (**135**) was isolated from the marine sponge *Xestospongia wiedenmayeri* and inhibits cholesteryl ester transfer protein (CETP).<sup>53</sup> Formal synthesis of (+)-**135** from (8a*S*)-bicyclofarnesol (**67**)

was shown in Scheme 18.<sup>54</sup> The enzymatic reaction product (8a*S*)-**125** was converted to (8a*S*)-bicyclofarnesyl bromide (**130**) *via* (8a*S*)-**67** in the same way as above mentioned procedure. The reaction of an ate complex derived from 1,2,4-trimethoxybenzene with (8a*S*)-**130** gave the desired product (10*S*)-**134** in 56% overall yield from (8a*S*)-**67**. The synthesis of (+)-**135** from (10*S*)-**134** has already been achieved based on selective demethylation.<sup>55</sup>

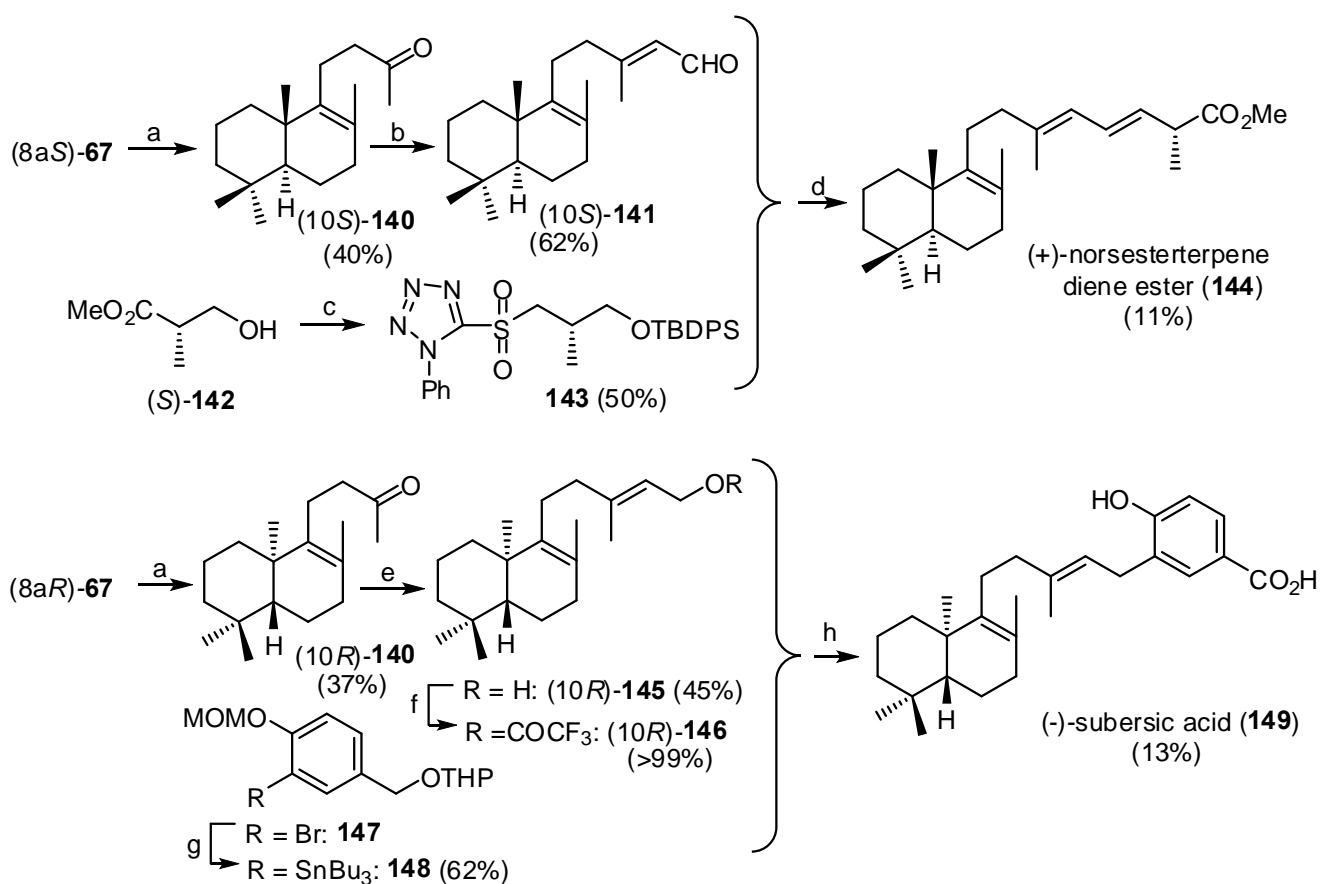
### 5.5. Syntheses of (+)-austrodoral and (+)-austrodoric acid

(+)-Austrodoral (**138**)<sup>56</sup> and (+)-austrodoric acid (**139**)<sup>57</sup> are two related norsesquiterpenes isolated from the skin extract of Antarctic dorid nudibranch *Austrodoris kerguelensis*. They possess a bicyclic structure with the rare carbon skeleton, which could biogenetically arise from a drimane type framework by a ring contraction process. Although the main products of the acid-catalyzed rearrangement of epoxides are typically carbonyl compounds, other compounds may be also formed depending on the nature of the epoxides, e.g., number of substituents, functional groups and steric structures. Epoxidation of (8a*S*)-bicyclofarnesol (**67**) gave a (8a*S*)- $\alpha$ -epoxybicyclofarnesol (**136**),<sup>58</sup> which was reacted with CF<sub>3</sub>COOH to afford a rearranged product (**137**) in 96% yield. The structure of **137** was confirmed by the fact that **137** was converted to (+)-austrodoric acid (**139**) as shown in Scheme 18.<sup>59</sup> NaBH<sub>4</sub> reduction of **137** followed by treatment NaIO<sub>4</sub> gave (+)-austrodoral (**138**) in 87% yield. Jones oxidation of **138** gave (+)-austrodoric acid (**139**) in 79% yield.

### 5.6. Synthesis of (+)-norsesterterpene diene ester

(+)-Norsesterterpene diene ester (**144**) was isolated from an Australian marine sponge, *Latrunculia brevis*, and its structure was determined by detailed spectroscopic analysis, chemical derivatization and degradation.<sup>60</sup> Our synthetic plan for (+)-**144** is based on synthesis of (13*E*,10*S*)- $\alpha,\beta$ -unsaturated aldehyde (**141**) followed by the selective construction of the (3*E*,5*E*)-diene moiety including a C(2)-stereogenic center in (+)-**144** as shown in Scheme 19.<sup>54</sup> Treatment of (8a*S*)-**67** with PBr<sub>3</sub> followed by acetoacetic ester synthesis gave methyl ketone (10*S*)-**140** [40% overall yield from (8a*S*)-**67**], which was subjected to a Horner-Emmons reaction to afford a 7:2 mixture of (13*E*)- and (13*Z*)- $\alpha,\beta$ -unsaturated esters. Dibal-H reduction of this mixture gave a mixture of (13*E*)- and (13*Z*)-allylic alcohol, which was separated to give (13*E*)-allylic alcohol. Dess-Martin oxidation of (13*E*)-allylic alcohol afforded the desired aldehyde (10*S*)-**141** in 62% overall yield from (10*S*)-**140**. For selective construction of the (3*E*,5*E*)-diene moiety including C(2) stereogenic center in (+)-**144**, a modified Julia coupling method using a chiral sulfone (**143**) was thought likely to be effective. Silylation of methyl (*S*)-3-hydroxy-2-methylpropionate (**142**) followed by reduction with LiBH<sub>4</sub> gave (*S*)-alcohol, which was treated with

1-phenyl-1*H*-terazole-5-thiol (PTSH) in the presence of  $\text{Ph}_3\text{P}$  and diethyl azodicarboxylate provided the (*S*)-sulfide. Oxidation of this sulfide gave the desired sulfone (**143**) in 50% overall yield from (*S*)-**142**. A modified Julia coupling of (10*S*)-**141** and **143** in the presence of lithium bis(trimethylsilyl)amide (LHMDS) afforded a 11:1 (*E*:*Z*) mixture of diene. Deprotection of the silyl group in this mixture followed by chromatographic separation provided the desired (3*E*)-diene alcohol, which was subjected to stepwise oxidation (formation of aldehyde and carboxylic acid) to give the desired (3*E*)-diene carboxylic acid. Finally, treatment of this (3*E*)-diene carboxylic acid with  $\text{CH}_2\text{N}_2$  gave the (+)-norsesterterpene diene ester (**144**) in 11% overall yield from (10*S*)-**141**.



Reagents : a; 1)  $\text{PBr}_3$  / pyridine /  $\text{Et}_2\text{O}$  2) methyl acetoacetate / *t*-BuOK / DMSO 3) 2*M*-NaOH / MeOH

b; 1)  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$  / NaH / THF 2)  $\text{HAl}(\textit{i}\text{-Bu})_2$  / toluene 3) separation

4) Dess-Martin reagent /  $\text{CH}_2\text{Cl}_2$  c; 1)  $t\text{-BuPh}_2\text{SiCl}$  / imidazole / DMF 2)  $\text{LiBH}_4$

3) 1-phenyl-1*H*-terazole-5-thiol /  $(\text{EO}_2\text{C-N}=\text{N})_2$  /  $\text{Ph}_3\text{P}$  / THF

4) 30%  $\text{H}_2\text{O}_2$  /  $(\text{NH}_4)_6\text{Mo}_7\text{O}_{24} \cdot 4\text{H}_2\text{O}$  d; 1)  $\text{LiN}(\text{Me})_2$  / THF 2)  $\text{Bu}_4\text{NF}$  3) separation

4) Dess-Martin reagent /  $\text{CH}_2\text{Cl}_2$  5)  $\text{NaClO}_2$  /  $\text{NaH}_2\text{PO}_4$  / 2-methyl-2-butene / *t*-BuOH 6)  $\text{CH}_2\text{N}_2$

e; 1)  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{CO}_2\text{Me}$  / NaH / THF 2)  $\text{HAl}(\textit{i}\text{-Bu})_2$  / toluene

f;  $(\text{CF}_3\text{CO})_2\text{O}$  / 2,6-lutidine /  $\text{CH}_2\text{Cl}_2$  g; 1) *t*-BuLi / THF 2)  $\text{Bu}_3\text{SnCl}$

h; 1)  $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$  / CuI / DMF 2) PPTS / MeOH 3)  $\text{MnO}_2$

4)  $\text{NaClO}_2$  /  $\text{NaH}_2\text{PO}_4$  / 2-methyl-2-butene / *t*-BuOH 5) 6*M* HCl / MeOH

Scheme 19

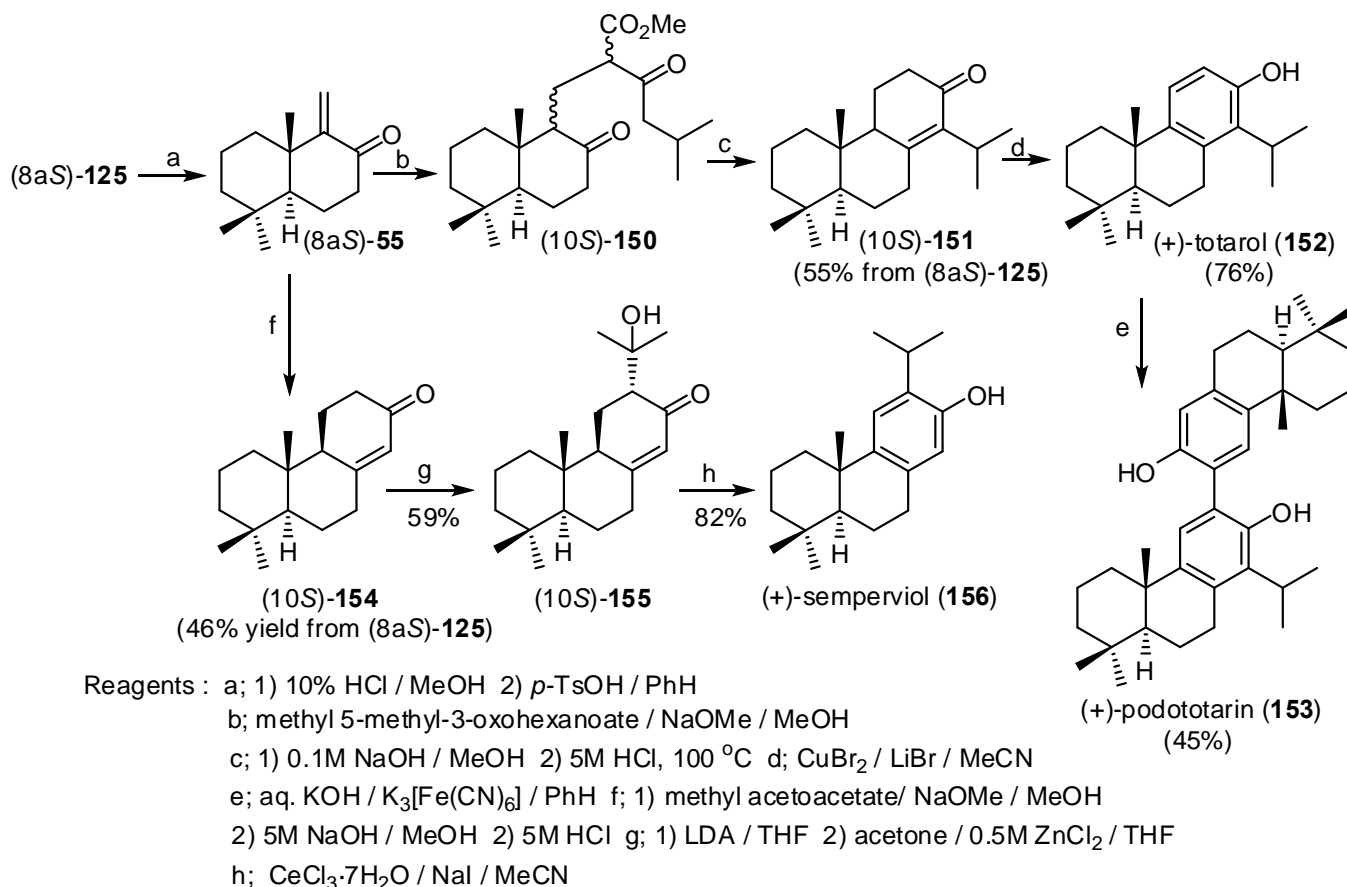
## 5.7. Synthesis of (-)-subersic acid

(-)-Subersic acid (**149**) was isolated from the Papua New Guinean sponge, *Suberea* sp. and is an inhibitor of human 15-lipoxygenase.<sup>61</sup> The structure of (-)-**149** was determined by extensive NMR analysis, and (5*R*,10*R*)-absolute structure of (-)-**149** was deduced based on the positive molar rotation of (-)-**149**. Our synthetic plan for (-)-**149** is based on a Stille coupling between allyl trifluoroacetate (10*R*)-**146** and arylstannane congener (**148**) as shown in Scheme 19.<sup>54</sup> The methyl ketone (10*R*)-**140** was synthesized from (8*aR*)-**67** in 37% overall yield from (8*aR*)-**67** in the same way as for preparation of (10*S*)-**140** from (8*aS*)-**67**. This methyl ketone was subjected to consecutive Horner-Emmons reaction and Dibal-H reduction to give (13*E*)-allylic alcohol (**145**) in 45% overall yield from (10*R*)-**140** in the same way as for preparation of (10*S*)-**141** from (10*S*)-**140**. The (13*E*)-allylic alcohol (**145**) was treated with (CF<sub>3</sub>CO)<sub>2</sub>O in 2,6-lutidine gave the corresponding trifluoroacetate (10*R*)-**146** in quantitative yield. Treatment of the reported aryl bromide congener (**147**) with *tert*-BuLi followed by addition of *n*-Bu<sub>3</sub>SnCl gave the desired stannane congener (**148**) in 62% overall yield from **147**. The reaction of allyl trifluoroacetate (10*R*)-**146** and **148** was carried out using Pd<sub>2</sub>(dba)<sub>3</sub>·CHCl<sub>3</sub> and CuI as an additive to give a 7:1 mixture (*E/Z* = 7:1) of the coupled products. Deprotection of the THP group in this mixture followed by stepwise oxidation (formation of aldehyde and carboxylic acid) gave a 9:1 mixture (*E/Z* = 9:1) of the corresponding carboxylic acid. Finally, deprotection of the MOM group in this carboxylic acid with 6M HCl followed by preparative HPLC separation gave (-)-subersic acid (**149**) in 13% overall yield from (10*R*)-**146**.

### 5.8. Syntheses of (+)-totarol, (+)-podototarol and (+)-semperviol

(+)-Totarol (**152**), a rare tricyclic diterpene phenol possessing an isopropyl group at the C(14) position, was first isolated as a major constituent of the heartwood of *Podocarpus totara* G. Benn and can also be isolated from a variety of other sources. It has been shown to have antibacterial activity against gram-positive bacteria, particularly methicillin-resistant *Staphylococcus aureus* (MRSA).<sup>62</sup> The structure of (+)-**152** was deduced on the basis of chemical and spectroscopic analysis, while the absolute structure was determined by ORD measurement and by direct correlation with dehydroabietic acid (**6**). (+)-Podototarol (**153**) was also isolated from the heartwood of *Podocarpus totara*,<sup>63</sup> and its structure was determined based on the synthesis from natural (+)-**152**. Straightforward syntheses of (+)-**152** and (+)-**153** are shown in Scheme 20.<sup>64</sup> The consecutive treatment of enzymatic reaction product (8*aS*)-**125** with 10% HCl and *p*-TsOH gave  $\alpha,\beta$ -unsaturated ketone (8*aS*)-**55** in quantitative yield, which was subjected to a Michael reaction with the anion obtained from the reaction of methyl 5-methyl-3-oxohexanoate with NaOMe to give a 2:1 diastereomeric mixture of (10*S*)-**150** in quantitative yield. Alkaline hydrolysis of this mixture followed by treatment with 5M HCl gave the aldol condensation product (10*S*)-**151** in 55% overall yield from (8*aS*)-**125**. Treatment of (10*S*)-**151** with CuBr<sub>2</sub> and LiBr gave (+)-totarol (**152**) in 76% yield. Oxidation of (+)-**152** with alkaline potassium ferricyanide [K<sub>3</sub>Fe(CN)<sub>6</sub>] gave (+)-podototarol (**153**)

in 45% yield. (+)-Sempervioid (**156**), a rare tricyclic diterpene phenol possessing an isopropyl group at the C(12) position, was isolated from *Cupressus sempervirens*.<sup>65</sup> Straightforward syntheses of (+)-**156** from (8a*S*)-**125** is shown in Scheme 20.<sup>64</sup> A Michael reaction of (8a*S*)-**55** derived from (8a*S*)-**125** with the anion obtained from the reaction of methyl acetoacetate with NaOMe gave a Michael addition product, which was subjected to alkaline hydrolysis followed by treatment with 5M HCl to provide the aldol



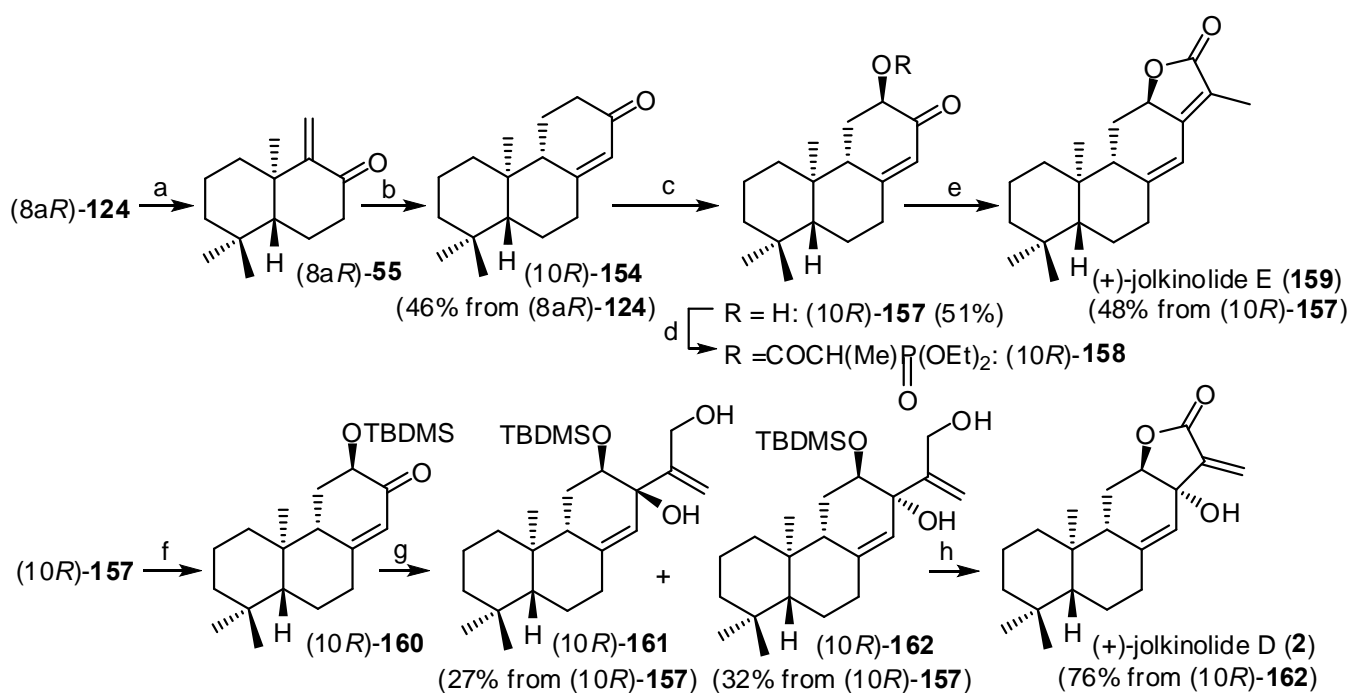
Scheme 20

condensation product (10*S*)-**154** in 46% overall yield from (8a*S*)-**125**. Lithiation of (10*S*)-**154** followed by treatment with acetone in the presence of ZnCl<sub>2</sub> gave aldol product (10*S*)-**155** in 59% yield. Finally, treatment of (10*S*)-**155** with a combination of CeCl<sub>3</sub> and NaI, followed by dehydration and aromatization, afforded (+)-sempervioid (**156**) in 82% yield.

### 5.9. Syntheses of (+)-jolkinolide D and (+)-jolkinolide E

Jolkinolides A, B, C, D (**2**) and E (**159**) are diterpenoids, which were isolated from the roots of *Euphorbia jolkini* Boiss.<sup>66</sup> The absolute structure of these compounds was determined by a chemical transformation to ferruginol (**8**), which possesses an abietane-type skeleton. The absolute structure of (+)-jolkinolide D (**2**) was also confirmed by X-ray crystallographic analysis. (+)-Jolkinolide D (**2**) exhibits cytotoxicity,

inhibits tumor invasion into the basement membrane, and induces apoptosis in tumor cells.<sup>67</sup> Straightforward syntheses of (+)-**2** and (+)-**159** from the enzymatic reaction product (8a*R*)-**124** are shown in Scheme 21.<sup>64</sup> Consecutive treatment of (8a*R*)-**124** with 10% HCl and *p*-TsOH gave  $\alpha,\beta$ -unsaturated ketone (8a*R*)-**55** in quantitative yield. A Michael reaction of (8a*R*)-**55** with the anion obtained from the reaction of methyl acetoacetate with NaOMe gave a Michael addition product, which was subjected to alkaline hydrolysis followed by treatment with 5M HCl to provide the aldol condensation product (10*R*)-**154** in 46% overall yield from (8a*R*)-**124**. Lithiation of (10*R*)-**154** followed by treatment with trimethylsilyl chloride (TMSCl) gave a silyl enol ether, which was treated with *m*-chloroperbenzoic acid (*m*-CPBA) followed by treatment with tetrabutylammonium fluoride (TBAF) to afford  $\alpha$ -hydroxy ketone (10*R*)-**157** in 51% overall yield from (10*R*)-**154**. Esterification of (10*R*)-**157** with 2-(diethylphosphono)propanoic acid in the presence of 4-dimethylaminopyridine (DMAP) and 1,3-dicyclohexylcarbodiimide (DCC) gave ester (10*R*)-**158**, which was treated with NaH to afford (+)-jolkinolide E (**159**) in 48% yield. Silylation of (10*R*)-**157** followed by treatment with a dianion



Reagents : a; 1) 10% HCl aq. / MeOH 2) *p*-TsOH / PhH  
 b; methyl 5-methyl-3-oxohexanoate / NaOMe / MeOH  
 c; 1) LDA / TMSCl / THF 2) *m*-CPBA / CH<sub>2</sub>Cl<sub>2</sub> 3) TBAF  
 d; 2-(diethylphosphono)propanoic acid / DMAP / DCC / CH<sub>2</sub>Cl<sub>2</sub> e; 60% NaH / DME  
 f; TBDMSCl / imidazole / DMF g; 2-iodoallyl alcohol / *n*-BuLi / Et<sub>2</sub>O  
 h; 1) TBAF / THF 2) MnO<sub>2</sub> / CH<sub>2</sub>Cl<sub>2</sub>

Scheme 21

obtained by the reaction of 2-iodoallyl alcohol and *n*-BuLi gave a diol (10*R*)-**161** [27% yield from (10*R*)-**157**] and a diol (10*R*)-**162** [32% yield from (10*R*)-**157**]. Desilylation of (10*R*)-**162** followed by treatment with MnO<sub>2</sub> gave (+)-jolkinolide D (**2**) in 76% overall yield from (10*R*)-**162**.

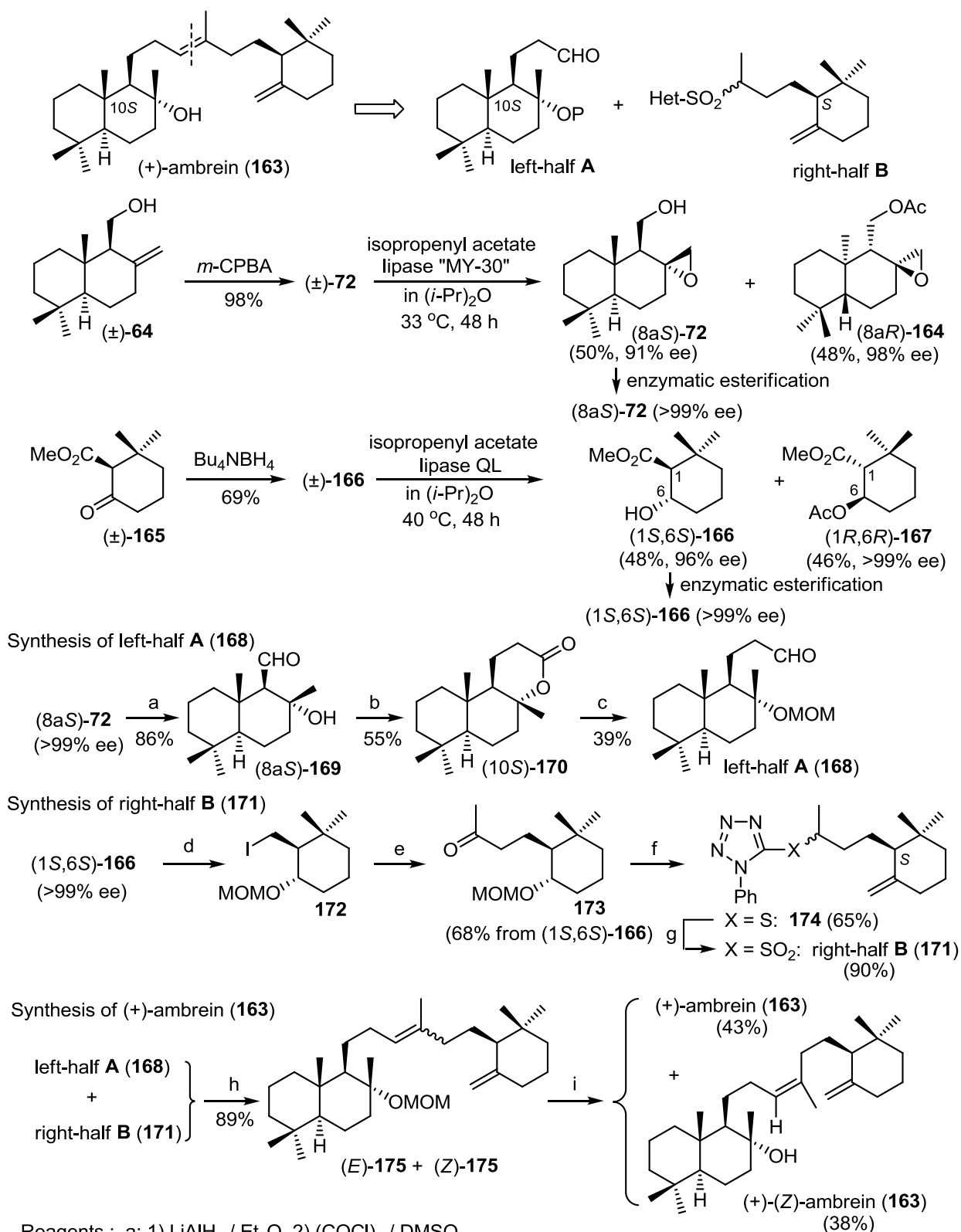
## 6. SYNTHESIS OF BOTH ENANTIOMERS OF EPOXYALBICANOL BASED ON ENZYMATIC RESOLUTION AND THEIR APPLICATION TO THE SYNTHESIS OF THE RELATED NATURAL PRODUCTS

### 6.1. Synthesis of (+)-ambrein

(+)-Ambrein (**163**) is a major constituent of ambergris, which is a metabolic of the sperm whale, and is used for the production of expensive perfumes.<sup>68</sup> However, the supply of ambergris has become very difficult, as commercial whaling is prohibited, and thus development of efficient synthesis of (+)-**163** is strongly desirable. Our synthetic plan for (+)-**163** is based on the double bond formation between the left-half **A** and the right-half **B** at the dotted line by the modified Julia coupling method as shown in Scheme 22.<sup>69</sup> In order to make two chiral building blocks, left-half (10*S*)-**A** and right-half (*S*)-**B**, both chiral (8*aS*)-epoxy alcohol **72** and (1*S*,6*S*)-β-hydroxy ester **166** appear to be useful starting materials, respectively.

#### 6.1.1 Syntheses of (8*aS*)-epoxyalbicanol (**72**) and (1*S*,6*S*)-β-hydroxy ester (**166**)

Epoxidation of (±)-albicanol (**64**) with *m*-CPBA gave (±)-epoxyalbicanol (**72**) in 98% yield, which was subjected to enzymatic esterification using isopropenyl acetate and lipase MY-30 from *Candida rugosa* to afford an acetate (+)-**164** (48% yield, 98% ee) and unchanged alcohol (-)-**72** (48% yield, 98% ee) and (50% yield, 91% ee). Enrichment of the enantiomeric excess (ee) of (-)-**72** was achieved by repeated enzymatic reaction. The absolute configuration at the C(8*a*)-position of (-)-**72** ([α]<sub>D</sub> -26.9 (c = 0.92, CHCl<sub>3</sub>)) was determined to be *S* by the direct comparison with the sign of [α]<sub>D</sub> of the reported (-)-(8*aS*)-**72** ([α]<sub>D</sub> -28.8 (c = 1.0, CHCl<sub>3</sub>)), thence that of (+)-**164** was confirmed to be *R*.<sup>69</sup> On the other hand, reduction of (±)-β-keto ester (**165**) with *n*-Bu<sub>4</sub>NBH<sub>4</sub> gave (±)-*trans*-β-hydroxy ester (**166**) in 69% yield, which was subjected to enzymatic esterification using isopropenyl acetate and lipase QL from *Alcaligenes* sp. to afford an acetate (**167**) (46% yield, >99% ee) and unchanged alcohol (+)-**166** (48% yield, 96% ee). Enrichment of the enantiomeric excess (ee) of (+)-**166** was achieved by repeated enzymatic reaction. The absolute structure of (+)-**166** was determined to be 1*S*, 6*S* by the fact that the present (+)-**166** was converted to (*S*)-γ-cyclogeraniol, thence that of an acetate (**167**) was confirmed to be 1*R*,6*R*.<sup>70</sup>



Reagents : a) 1) LiAlH<sub>4</sub> / Et<sub>2</sub>O 2) (COCl)<sub>2</sub> / DMSO

b) 1) Ph<sub>3</sub>P=CHCO<sub>2</sub>Me / PhH 2) H<sub>2</sub> / 20% Pd(OH)<sub>2</sub> / MeOH c) 1) LiAlH<sub>4</sub> / Et<sub>2</sub>O

2) Ac<sub>2</sub>O / DMAP / pyridine 3) MOM-Cl / *i*-Pr<sub>2</sub>NEt 4) K<sub>2</sub>CO<sub>3</sub> / MeOH 4) PDC / CH<sub>2</sub>Cl<sub>2</sub>

d) 1) LiAlH<sub>4</sub> / Et<sub>2</sub>O 2) MOM-Cl / *i*-Pr<sub>2</sub>NEt 3) I<sub>2</sub> / Ph<sub>3</sub>P / imidazole / THF

e) 1) MeCOCH<sub>2</sub>CO<sub>2</sub>Me / NaOMe / MeOH, 90 °C 2) 6M NaOH, 100 °C f) 1) NaBH<sub>4</sub> / MeOH

2) 1-phenyl-1*H*-tetrazole-5-thiol / (EtO<sub>2</sub>C-N=)<sub>2</sub> / Ph<sub>3</sub>P / THF 3) *conc.* HCl / MeOH 4) PDC

5) Ph<sub>3</sub>P<sup>+</sup>Me Br<sup>-</sup> / *t*-BuOK / toluene g) 30% H<sub>2</sub>O<sub>2</sub> / (NH<sub>4</sub>)<sub>6</sub>Mo<sub>7</sub>O<sub>24</sub>·4H<sub>2</sub>O / EtOH

h) LiN(SiMe<sub>3</sub>)<sub>2</sub> / THF i) 2M HCl / 80% AcOH aq.

Scheme 22

### 6.1.2 Synthesis of left-half A (168)

Reduction of enantiomerically pure (8a*S*)-**72** followed by Swern oxidation gave an aldehyde (8a*S*)-**169** in 86% overall yield, which was subjected to Wittig reaction to afford  $\alpha,\beta$ -unsaturated ester. Catalytic hydrogenation of  $\alpha,\beta$ -unsaturated ester gave  $\delta$ -lactone (10*S*)-**170** in 55% overall yield from (8a*S*)-**169**. LiAlH<sub>4</sub> reduction of (10*S*)-**170** gave a diol, which was subjected to selective acetylation of the primary hydroxyl group of the diol to afford a mono-acetate. Treatment of the mono-acetate with methoxymethyl chloride (MOM-Cl) gave MOM ether, which was subjected to consecutive alkaline hydrolysis and PDC oxidation to provide left-half A (**168**) in 39% overall yield from (10*S*)-**170**.

### 6.1.3 Synthesis of right-half B (171)

Treatment of enantiomerically pure (1*S*,6*S*)-**166** with MOM-Cl gave the corresponding MOM ether, which was reduced with LiAlH<sub>4</sub> to give an alcohol. Conversion of the alcohol to an iodide (**172**) using I<sub>2</sub>/Ph<sub>3</sub>P/imidazole reagent system followed by acetoacetic ester condensation gave a ketone (**173**) in 68% overall yield from (1*S*,6*S*)-**166**. NaBH<sub>4</sub> reduction of **173** followed by treatment with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) in the presence of Ph<sub>3</sub>P and diethyl azodicarboxylate provided a diastereomeric mixture of (*S*)-sulfide (**174**) in 65% overall yield from **173**, which was subjected to oxidation to give the desired right-half B (**171**) in 90% yield.

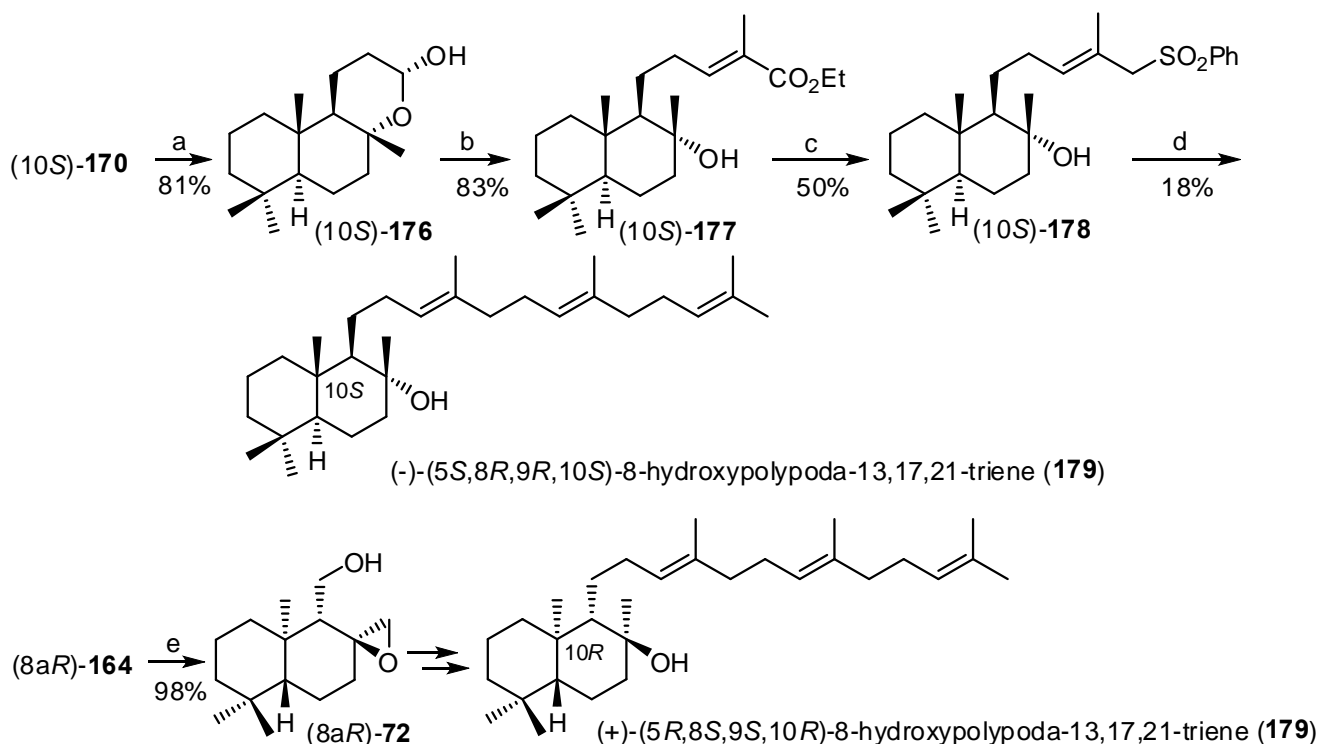
### 6.1.4 Modified Julia coupling of left-half A (168) with right-half B (171)

The reaction of left-half A (**168**) with right-half B (**171**) in the presence of 1M solution of lithium bis(trimethylsilyl)amide (LHMDS) in THF gave a mixture (*E/Z* = 1/1) of **175** in 89% yield. Deprotection of the MOM group in **175** gave (*E*)-(+)-ambrein (**163**) (43% yield) and (*Z*)-(+)-ambrein (**163**) (38% yield).

## 6.2. Synthesis of (-)-(8*R*,10*S*)- and (+)-(8*S*,10*R*)-8-hydroxypolypoda-13,17,21-triene

Novel triterpene alcohol 8 $\alpha$ -hydroxypolypoda-13,17,21-triene (**179**) was isolated from a fern, *Polypodiodes fomtosana*.<sup>71</sup> The occurrence of this type of alcohol from nature is important from the mechanistic point of view of the biosynthesis of lanosterol from 2,3-oxidosqualene *via* a cationic intermediate. The structure of **179** including its absolute configuration has been elucidated as 8 $\alpha$ -hydroxypolypoda-13,17,21-triene on the basis of spectral and chemical evidence. In order to reconfirm the absolute structure of natural **179**, the synthesis of both enantiomers of **179** was necessitated because of the low value of optical rotation ( $[\alpha]_D -0.9$ ). The key optically active intermediate for the synthesis of (-)-**179** and (+)-*ent*-**179** appeared to be the enzymatic products (8a*S*)-**72** and (8a*R*)-**164**. An outline of the synthesis of (8*R*,10*S*)-8-hydroxypolypoda-13,17,21-triene (**179**) from (8a*S*)-epoxyalbicanol (**72**) is

depicted in Scheme 23,<sup>72</sup> which involves the preparation of  $\alpha,\beta$ -unsaturated ester (10*S*)-**177** by Wittig condensation followed by coupling reaction of the sulfone (10*S*)-**178** derived from (10*S*)-**177** and *trans*-geranyl bromide. The synthesis of (+)-*ent*-**179** from (8*aR*)-**164** is fundamentally carried out in the same way as for the synthesis of (8*R*,10*S*)-**179** and the synthesis of (+)-*ent*-**179** was omitted. Dibal-H reduction of  $\delta$ -lactone (10*S*)-**170** derived from (8*aS*)-**72** (Scheme 22) gave lactol (10*S*)-**176** in 81% yield, which was subjected to Wittig condensation with  $\text{Ph}_3\text{P} = \text{C}(\text{Me})\text{CO}_2\text{Et}$  to afford *trans*- $\alpha,\beta$ -unsaturated ester (10*S*)-**177** in 83% yield. The reaction of (10*S*)-**177** with trimethylsilyl trifluoromethanesulfonate (TMSOTf) in the presence of (*i*-Pr)<sub>2</sub>NEt and Et<sub>3</sub>N gave the corresponding silyl ether, which was reduced with Dibal-H to provide an allyl alcohol. The reaction of the allyl alcohol with MsCl in the presence of LiCl and 2,6-lutidine gave the corresponding allyl chloride, which was treated with  $\text{PhSO}_2\text{Na}\cdot 2\text{H}_2\text{O}$  to afford the desired sulfone (10*S*)-**178** in 50% overall yield from (10*S*)-**177**. Lithiation of sulfone (10*S*)-**178** with LDA followed by treatment with *trans*-geranyl bromide gave a diastereomeric mixture of alkylated product, which was treated with 5% Na-Hg to afford (-)-(8*R*,10*S*)-8-hydroxypolypoda-13,17,21-triene (**179**) ( $[\alpha]_{\text{D}} -0.6$ , ( $c = 0.75$ ,  $\text{CHCl}_3$ )) in 18% overall yield from (10*S*)-**178**. On the other hand, the synthesis of (+)-*ent*-**179** from (8*aR*)-**164** was carried out. Alkaline hydrolysis of the enzymatic reaction product



Reagents : a;  $\text{HAl}(\textit{i}\text{-Bu})_2$  / toluene b;  $\text{Ph}_3\text{P}=\text{C}(\text{Me})\text{CO}_2\text{Et}$  / PhH c; 1) TMSOTf / (*i*-Pr)<sub>2</sub>NEt / Et<sub>3</sub>N  
2)  $\text{HAl}(\textit{i}\text{-Bu})_2$  / toluene 3) MsCl / LiCl / 2,6-lutidine /  $\text{NaHCO}_3$  / DMF 4)  $\text{PhSO}_2\text{Na}\cdot 2\text{H}_2\text{O}$  / DMF  
d; 1) LDA / *trans*-geranyl bromide / THF 2) 5% Na-Hg / MeOH e;  $\text{K}_2\text{CO}_3$  / MeOH

Scheme 23

(8*aR*)-**164** gave (8*aR*)-epoxyalbicanol (**72**) in 98% yield, which was converted to (+)-(8*S*,10*R*)-8-hydroxypolypoda-13,17,21-triene (**179**) ( $[\alpha]_D +0.5$ , ( $c = 0.72$ ,  $\text{CHCl}_3$ )). Thus, the absolute structure of natural (-)-**179** was determined to be 5*S*,8*R*,9*R*,10*S* configurations.

## 7. CONCLUSION

The practical synthesis of both enantiomers of chiral intermediate for the syntheses of the natural products possessing the bicyclo[4.4.0]ring system with 4,4,10-trimethyl groups and their application to the total syntheses of the related natural products possessing biological activity were achieved. Chiral induction was carried out based on enzymatic resolution or optical resolution using chiral auxiliary.

## ACKNOWLEDGMENTS

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