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SYNTHESIS OF TERPENOID COMPOUNDS FROM α-SANTONIN

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CONTENTS

1. INTRODUCTION

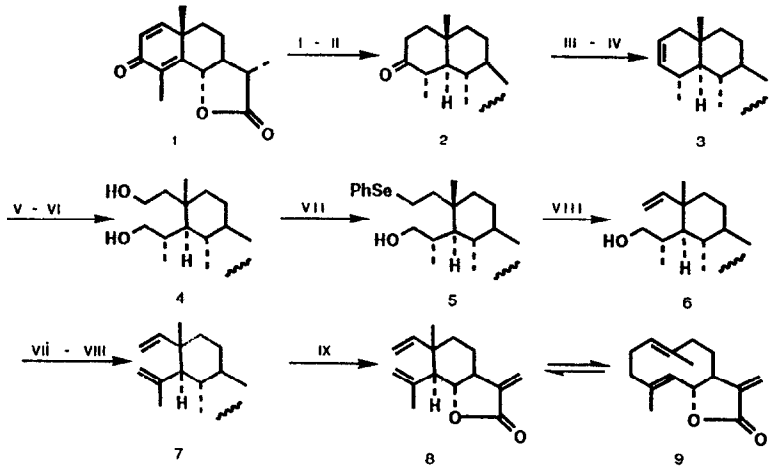
A number of closely related sesquiterpenoid lactones possessing the eudesmane skeleton are found in various Asian plants of the genus Artemisia. The most abundant and the most important is α-santonin **1** which has been extensively used in medicine, particularly in India, to combat intestinal worms. The total synthesis of α-santonin has been pursued by a number of organic chemists.[1] Owing to the presence of many diverse functional groups, α-santonin has been selected as the starting material for the synthesis of many naturally occurring terpenoid compounds. This report summarizes the literature results.

2. LITERATURE RESULTS

2.1. *Costunolide and dihydrocostunolide*

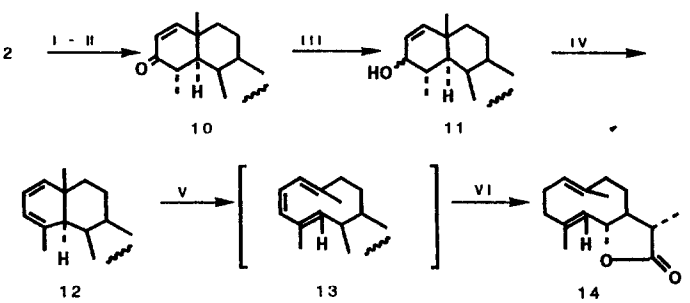
Costunolide **9** and dihydrocostunolide **14** are members of the germacrane class of sesquiterpenes whose syntheses present a challenge due to the elaboration of the cyclodecadiene unit. The synthesis[2,3]

of costunolide **9** is described in Scheme 1. α-Santonin **1** was converted to saturated ketolactone **2** whose tosylhydrazone derivative gave olefin **3** through the Shapiro olefin reaction indicating that the enolate played the role of a protecting group for the lactone moiety. The diol **4** surprisingly yielded only the monoselenide **5** and not the expected bis selenide. The transformation of the monoselenide **5** to saussurea lactone **7** and dihydrosaussurea lactone **8** was achieved via the olefinic alcohol **6**. The Cope rearrangement of lactone **8** gave the costunolide **9**. This is unusual because the formation of the six membered ring isomer is not favored by the cyclodecadiene–divinylcyclohexane equilibrium.



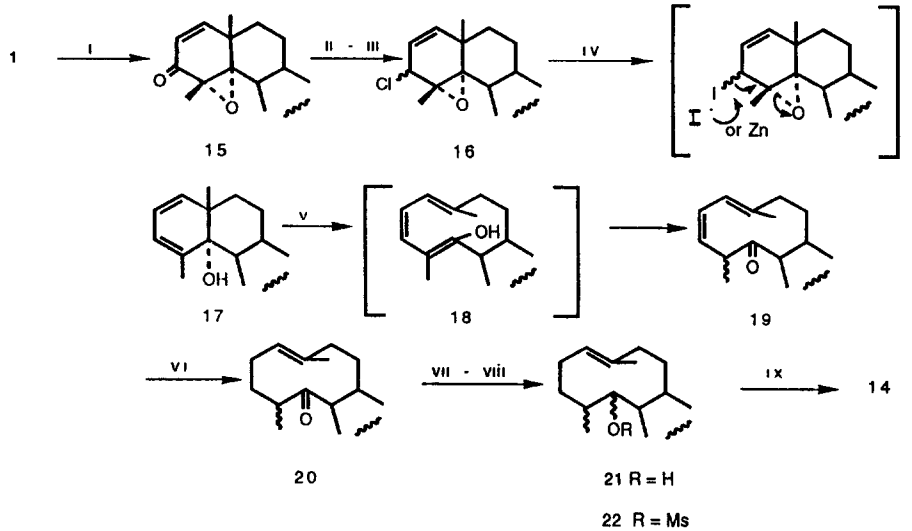
Scheme 1. (i) H_2, 2% Pd–$SrCO_3$, (ii) HCl–EtON, (iii) $TsNHNH_2$, BF_3Et_2O, (iv) LDA, THF, (v) O_3, CH_2Cl_2–MeOH (1 : 1), (vi) $NaBH_4$, (vii) $NO_2C_6H_4SeCN$, Bu_3P, THF, (viii) 50% H_2O_2, THF, (ix) LDA, PhSeSePh, H_2O_2, THF, −78°C.

Corey and Hortmann[4] developed an excellent preparation of dihydrocostunolide **14** from α-santonin (Scheme 2). Tetrahydrosantonin **2** (Scheme 1) was converted to the α,β-unsaturated ketone **10** and then reduced to allylic alcohol **11**. Other reducing agents, like sodium borohydride or lithium *t*-butoxide did not give the desired product. The irradiation of the diene **12** to carbocyclic triene **13** was carried out below 15°C in methanol. The thermally unstable triene **13** on hydrogenation at −18°C afforded a mixture of products from which dihydrocostunolide **14** was obtained by chromatographic purification on silicic acid at −23°C to −25°C. The yield was poor when the chromatographic purification was carried out at room temperature. Grieco[2] reported the formation of a mixture of saussurea lactone **7** and dihydrocostunolide **14** on thermolysis of saussurea lactone **7**.



Scheme 2 (i) Br_2, (ii) LiBr/DMF, (iii) $Al(O\text{-}iPr)_3$, (iv) Py–Al_2O_3, (v) hν, (vi) H_2, Ra–Ni, MeOH, −18°C.

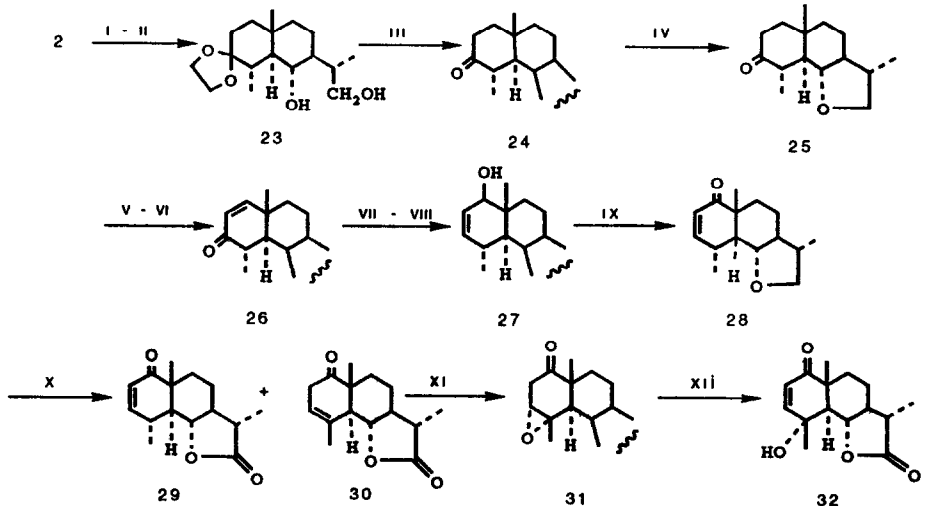
Japanese chemists developed an alternative synthesis[5] of dihydrocostunolide **14** from α-santonin as depicted in Scheme 3. The epoxide **15**, derived from α-santonin gave on reduction and tosylation the unexpected chloroepoxide **16**, which was reduced to the dienol **17**. Irradiation of the dienol **17** (7W low pressure mercury lamp, methanol, 15°C) initially gave the cyclodecatrienol **18** which isomerized to the diene **19** as a 5 : 1 : 1 mixture of stereoisomers. Hydrogenation of the major isomer yielded the ketolactone **20** which was converted to the mesyl derivative **22** via the alcohol **21**. The mesylate **22** was converted to dihydrocostunolide **14** with tetra-*n*-butylammonium oxalate. Other bases were unsuccessful in bringing about this transformation.



Scheme 3. (i) MCPBA, (ii) $LiAlH_4$, (iii) *p*-TsCl, (iv) NaI–Zn, (v) hν, (vi) H_2, Pd/C, (vii) $NaBH_4$, (viii) MsCl/Py, (ix) Tetra-butylammonium oxalate (TBAO)

2.2. *Vulgarin and C_4-epivulgarin*

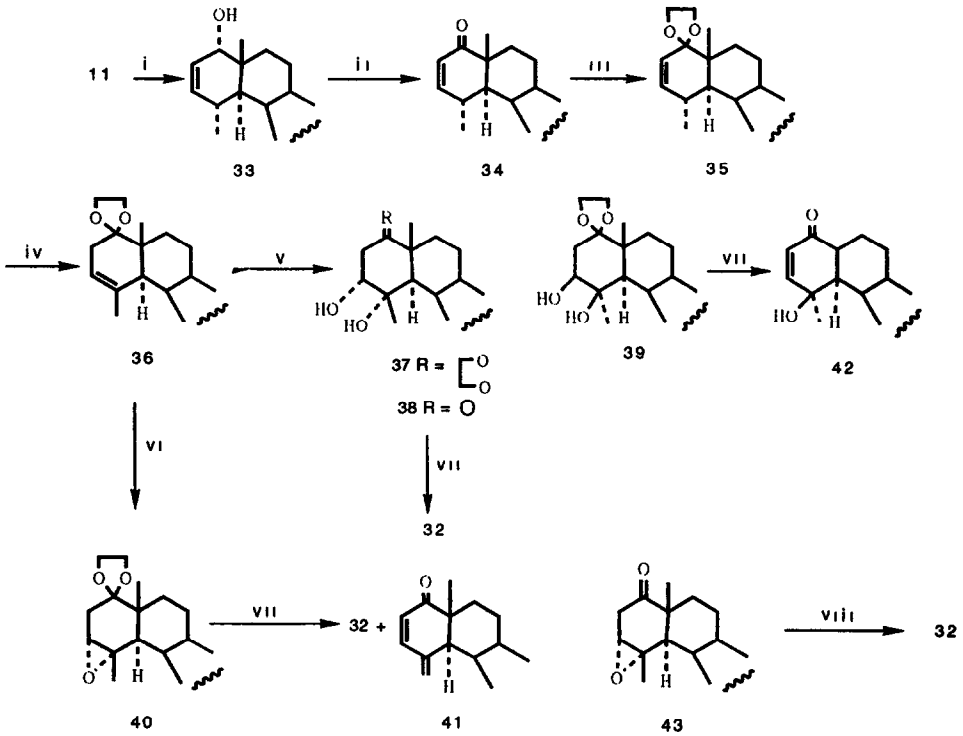
Rao and collaborators[6] converted α-santonin into the sesquiterpene lactone vulgarin **32** as shown in Scheme 4. Tetrahydrosantonin **2** was converted to the α,β-unsaturated ketone **28** as illustrated.



Scheme 4. (i) $(CH_2OH)_2$, H^+, (ii) $LiAlH_4$, (iii) H_3O^+, (iv) *p*-TsCl, (v) Br_2 AcOH, (vi) Collidine, (vii) 30% H_2O_2/NaOH, (viii) 80% N_2H_4, (ix) CrO_3, H_2SO_4, (x) CrO_3/AcOH, (xi) $PhCO_3H$, (xii) KOH.

Oxidation of **28** produced a mixture of lactones **29** and **30** which, without separation, was epoxidized to **31**. On treatment with alkali this was converted to vulgarin **32**.

Ando and coworkers[7] developed a synthesis of vulgarin **32** which is shown in Scheme 5. The alcohol **11** underwent allylic rearrangement to **33** which was then converted to the ketal **35** in a straightforward manner. Heating **35** at 145°C for 10 min gave **36** by isomerization of the double bond. Under more vigorous conditions the double bond of **36** isomerized to an *exo* position. Oxidation of **36** with osmium tetroxide gave a mixture of ketal **37** (32.3%), ketone **38** (12.3%) and the ketal **39** (26.2%). The formation of these products, resulting from attack from either the α or β-face, can be explained on the basis of competitive steric hindrance between the angular methyl group and the oxygen of the acetal group. Epoxidation of **36** led to the formation of **40** in quantitative yield, the reaction occurring from the α-face. It is reasonable to assume that the hydrogen bonding between *m*-chloroperbenzoic acid and the oxygen of the acetal group directs the attack from the α-face. Both the ketal **37** and the ketone **38** gave vulgarin **32** (86.6%) on treatment with boiling acetic acid (50%) for 74 hr. Similar treatment of the epoxide **40** gave vulgarin **32** (30.3%) together with the dienone **41**, while the ketal **39** gave C_4-epivulgarin **42** (86.5%).



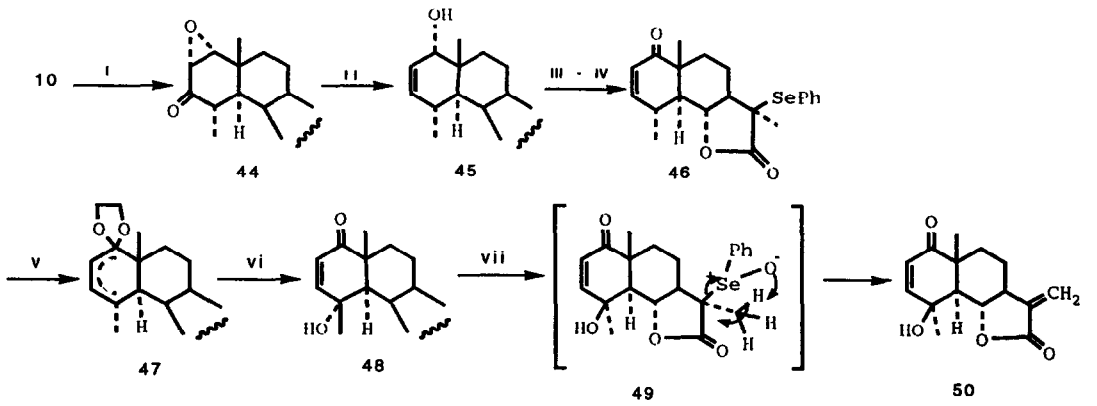
Scheme 5. (i) 2M HCl, THF, (ii) CrO_3, 2Py, CH_2Cl_2, (iii) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, (iv) 145°C, *p*-TsOH, $(CH_2OH)_2$, (v) OsO_4, aq. dioxane, H_2S, (vi) MCPBA, (vii) 50% aq. AcOH, (viii) ACOH

An improved synthesis of vulgarin **32** from the ketal **37** was reported by Ando.[8] The ketal was converted to the ketone **38** with acid, which on epoxidation gave the α-epoxide **43** in quantitative yield. Treatment of **43** with silica gel yielded **32** (90%). Ando[8] also observed that passing oxygen through a boiling 50% aqueous acid solution of **37** gave **32** (50%).

2.3. *Arglanine, santamarine, tuberiferine and artecalin*

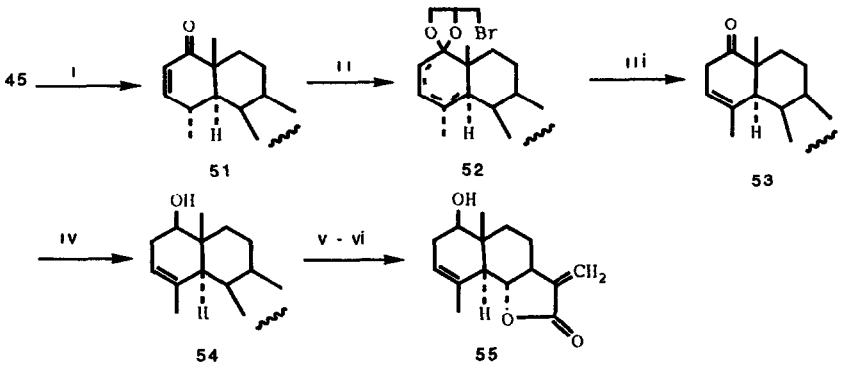
A number of sesquiterpenes containing α-methylene-γ-lactones have been prepared from α-santonin. The synthesis[9] of arglanine **50** is shown in Scheme 6. The α,β-unsaturated ketone **10** was

converted to the enone **46** as shown. Ketalization of enone **46** produced a mixture of isomeric ketals **47** which could not be separated. Oxidative deketalization of **47** to **48** was accomplished by bubbling oxygen through the reaction mixture. Under nitrogen **47** reacted to give **46**. Oxidation of **48** gave the oxide **49** which was eliminated to give arglanine **50**. An alternative synthesis of arglanine **50** from the ketal **37** was developed by Ando[7] following the procedure of Yamakawa.[9]



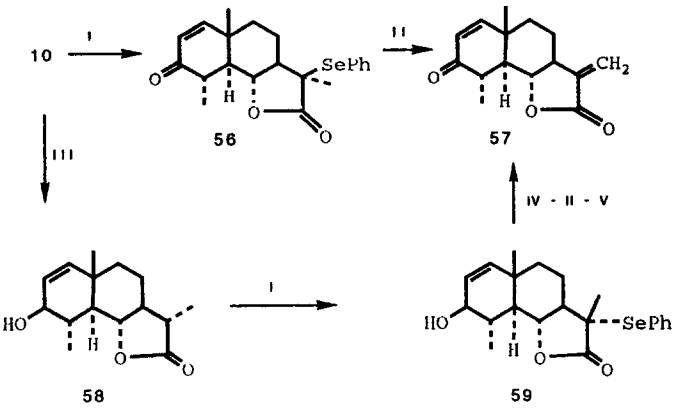
Scheme 6. (i) H_2O_2 (30%), KOH, (ii) N_2H_4, EtOH/ACOH, (iii) active MnO_2, (iv) LDA, THF, PhSeSePh, (v) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, (vi) O_2, (vii) H_2O_2 (30%), THF–ACOH, 0°C.

The successful transformation of α-santonin into santamarine **55** has been reported by Yamakawa[9] (Scheme 7). The alcohol **45**, described in Scheme 6, was utilized as starting material and was transformed into santamarine **55** by a procedure similar to that shown in Scheme 6.



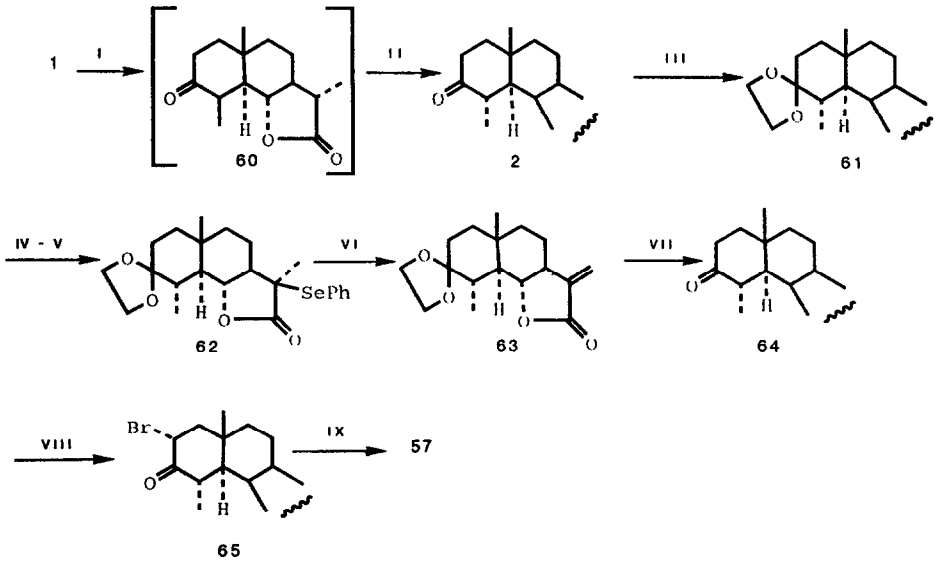
Scheme 7. (i) CrO_3/H_2SO_4, (ii) bromoglycol, (iii) Zn/MeOH, (iv) $NaBH_4$/MeOH, (v) LDA/THF, PhSeSePh, (vi) H_2O_2 (30%), THF–ACOH, 0°C.

The bioactive sesquiterpene lactone tuberiferine **57** was synthesized[10] from α-santonin as shown in Scheme 8. Most of the steps were carried out by reactions already described. The phenylselenylation of ketone **10** resulted in a very poor yield compared with the phenylselenylation of the allylic alcohol **58**. The yield of tuberiferin **57** was considerably improved when the allylic alcohol **58** was oxidized with manganese oxide rather than with Jones reagent.



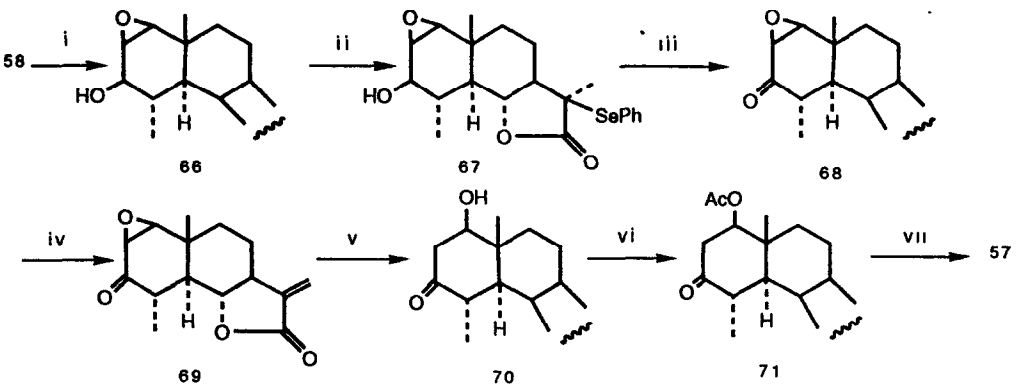
Scheme 8 (i) LDA, THF, PhSeSePh, (ii) H_2O_2 (30%), THF–ACOH, (iii) $LiAlH_4$, (iv) activated MnO_2, (v) Jones reagent.

Ando and coworkers[11] developed an alternative synthesis of tuberiferine **57** from α-santonin (Scheme 9).



Scheme 9. (i) H_2/2% Pd–$SrCO_3$, AcOET, (ii) HCl, EtOH, (iii) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, (iv) LDA, THF, (v) PhSeSePh, HMPA, THF, (vi) H_2O_2 (30%), AcOH, THF, (vii) 2% aq. AcOH–EtOH, (viii) 1.1 equiv. of PTAB, THF, −6°C, (ix) Li_2CO_3, LiBr, DMF, 123–124°C.

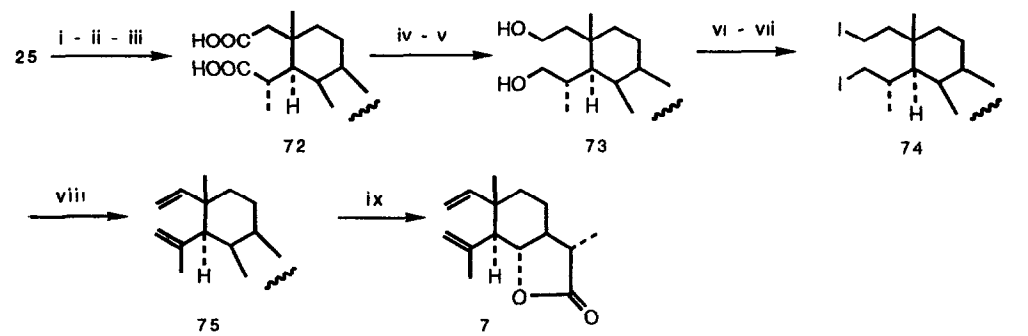
The sesquiterpene lactone artecalin **70** has been prepared[10] from α-santonin as described in Scheme 10, which shows the conversion of **58** to **70**. The attractive aspect of this synthesis is the stereoselective epoxidation of **58** with *t*-butylhydroperoxide in the presence of vanadyl acetyl acetonate to give the β-epoxide **67** (47%) and enone **10** (39%). The epoxyketone **69** was reductively opened with zinc dust in benzene containing a few drops of acetic acid.



Scheme 10. (i) *t*-butyl hydroperoxide/vanadyl acetyl acetonate, (ii) LDA, THF, PhSeSePh, HMPA, THF, (iii) activated MnO_2, (iv) H_2O_2 (30%), AcOH, THF, (v) Zn dust/C_6H_6/a few drops of ACOH, (vi) $(MeCO)_2O$/Py, (vii) NaOQc/EtOH.

2.4. *Saussurea lactone*

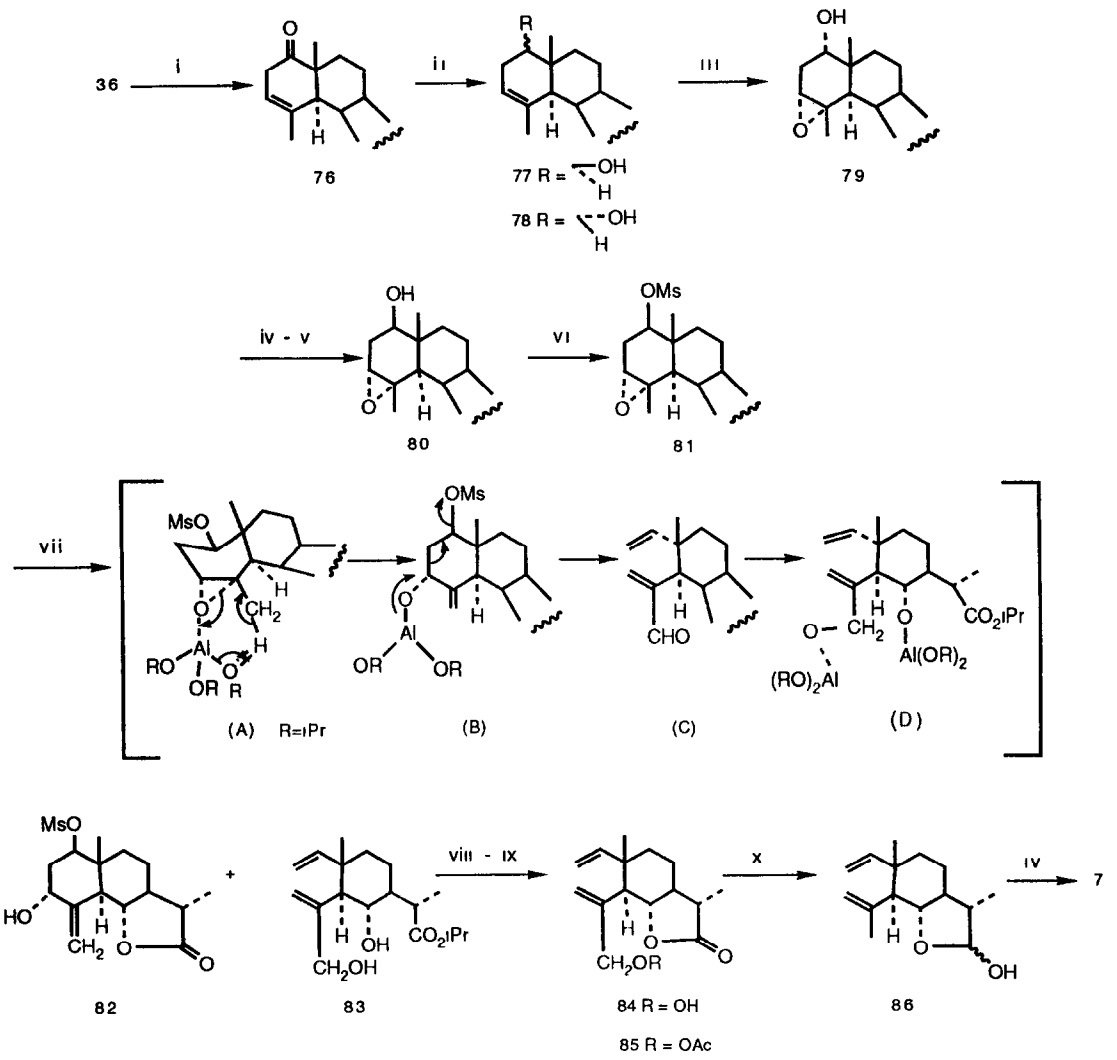
The saussurea lactone **7** was synthesized from α-santonin both by Rao[12] (Scheme 11) and Ando[13] (Scheme 12). The lactone **25** (see Scheme 6) was converted to the benzyl enolether which, on ozonolysis followed by oxidative workup, gave the diacid **72**. Esterification of **72** and reduction gave the diol **73**. The diol **73** was tosylated and the ditosylate converted to the diiodide **74** which on *cis*-elimination gave the diene **75**. Oxidation of **75** gave **7**. The oxidative cleavage of ozonide resulting from **25** was carried out under alkaline conditions since under acidic conditions some lactone was formed.



Scheme 11. (i) PhCHO, OH^-, (ii) O_3, (iii) H_2O_2, OH^-, (iv) CH_2N_2, (v) $LiAlH_4$, (vi) TsCl, Py, (vii) NaI, (viii) *t*-BuOK/DMSO, (ix) CrO_3/ACOH.

The acetal **36** in Scheme 12, was deprotected and the resultant enone **76** reduced to a 4 : 1 mixture of epimeric alcohols **77** and **78**. Epoxidation of this mixture gave **79** and **80** in 19% and 74% yields, respectively. The minor epoxide **79** was readily converted to **80**. The alcohol **80** was mesylated and the resulting mesylate **81** was treated with aluminium isopropoxide in boiling toluene for 72 hr to give the hydroxymesylate **82** (9%) and the fragmentation product **83** (68%). The relative proportion of the products **82** and **83** depends on the period of heating. The fragmentation can be mechanistically rationalized as follows. Complexation of aluminium isopropoxide with the epoxide ring oxygen **A** is followed by concomitant deprotonation of the methyl group and ring openings to give **B**. The intermediate **B** can be fragmented by loss of the mesylate to give the diene aldehyde **C**. Meerwein–

Pondorf reduction of **C** via **D** gave, after hydrolysis of the product, **83**. Fragmentation was not observed on treatment of the mesylate **81** with LDA or t-BuOK. Hydrolysis of **83** followed by lactonization afforded **84**. Acetylation of **84** gave **85** which was reduced to give a diastereoisomeric mixture of hemiacetal **86**. Oxidation of this mixture gave saussurea lactone **7**.

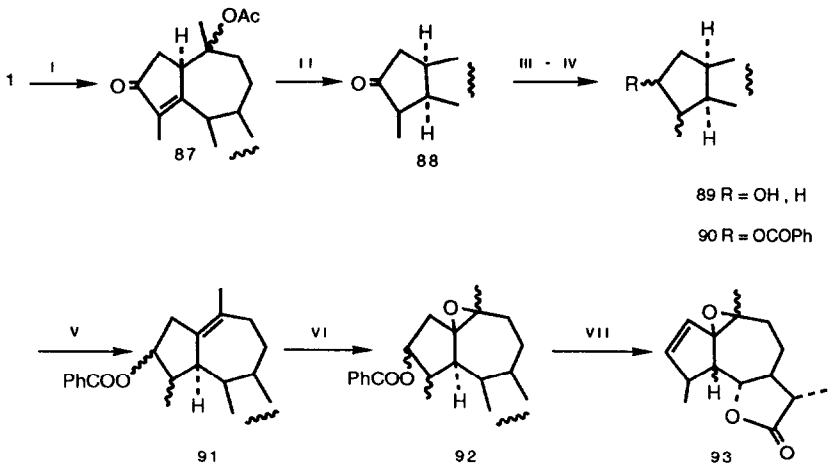


Scheme 12. (i) 50% AcOH, reflux, (ii) $LiAl(t\text{-}BuO)_3H$, (iii) MCPBA, (iv) CrO_3, 2Py, CH_2Cl_2, (v) $Zn(BH_3)_2$, (vi) MsCl/Py, (vii) $Al(i\text{-}PrO)_3$, toluene, (viii) 1M, KOH, EtOH, 50°C, (ix) *p*-TsOH, C_6H_6, reflux, (x) Li/liq. NH_3

2.5. *Arborescin*

The transformation of α-santonin into terpene lactone arborescin **93** has been achieved by Czechoslovakian scientists[14] as depicted in Scheme 13. The conversion of α-santonin into O-acetyldihydroisophotosantonic lactone **87** was effected by Barton's procedure.[15] The saturated lactone **88** on reduction yielded a mixture of alcohols **89** whose benzoate derivative **90** gave the

olefin **91** on treatment with a Lewis acid. Pyrolysis of the epoxide **92** gave arborescin **93**. The synthesis does not provide any evidence regarding the stereochemistry of the epoxide ring of **93**.



Scheme 13 (i) hν, HOAc, (ii) H_2, Pd/C, (iii) $NaBH_4$, (iv) PhCOCl, (v) BF_3, Et_2O, (vi) $PhCO_3H$, (vii) 210°C.

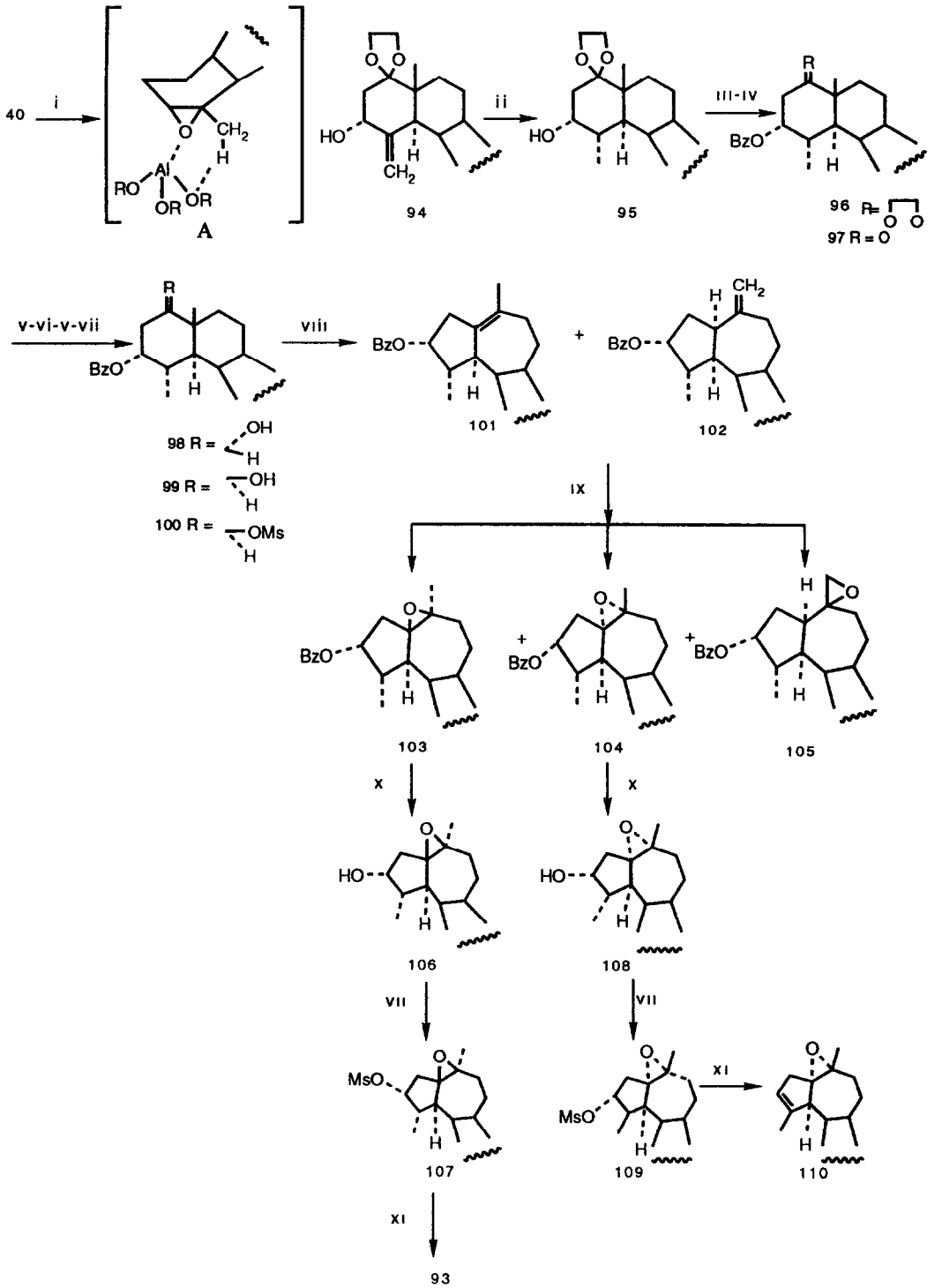
Ando and coworkers[16] developed an alternative synthesis of arborescin **93** from α-santonin which determined the β-orientation of the epoxide ring (Scheme 14). The epoxide **40** (Scheme 5) on reduction afforded the allylic alcohol **94**. The high regioselectivity of this reaction is probably due to the formation of the possible intermediate **A**. The sequence **95** → **100** was uneventful except that the alcohol **99** could not be converted to the tosyl derivative, probably due to the steric hindrance imposed by the angular methyl group and α-axial benzoyl group. It could, however, be converted to the mesyl derivative **100** which, under solvolytic rearrangement, yielded a mixture of *endo* and *exo*-cyclic olefins **101** and **102** in a ratio of 2 : 1. Epoxidation of the mixture of olefins with excess *m*-chloroperbenzoic acid yielded a mixture of the epoxides **103** (30%), **104** (38%) and **105** (20%). Epoxidation with 0.5 molar equivalent of *m*-chloroperbenzoic acid only oxidized the *endo* olefin **101**, yielding a mixture of epoxides **103** (22%) and **104** (29%), which were readily transformed to arborescin **93** and its epimer **110**, respectively.

2.6. *Desacetoxymatricarin, achillin and dihydroarbiglovin*

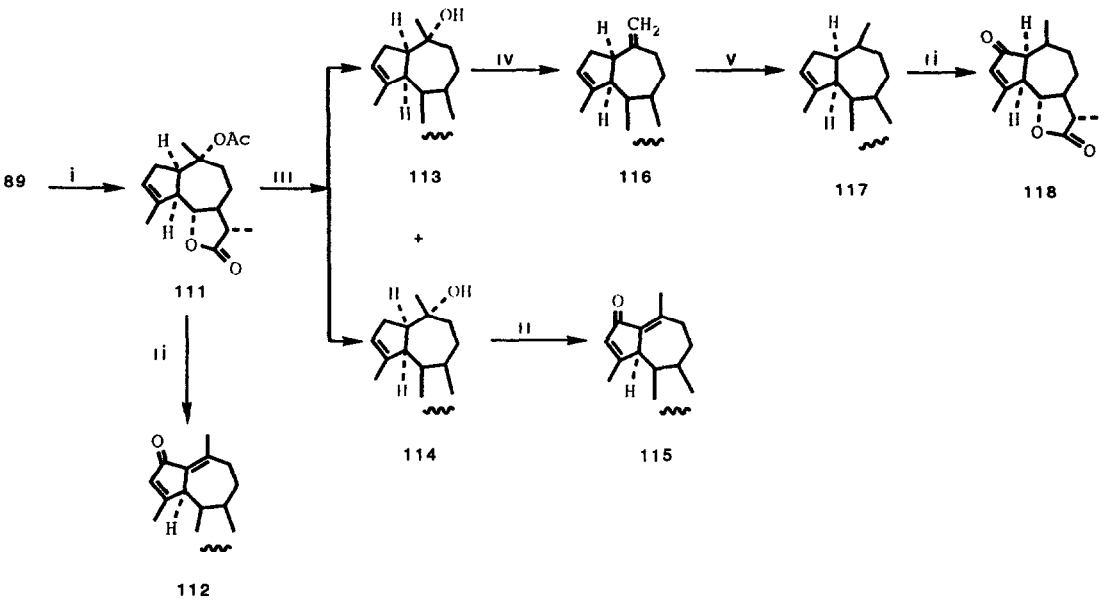
White[17] developed a synthesis of desacetoxymatricarin **112** from the alcohol **89**. This alcohol was also utilized by Marx[18,19] for the synthesis of achillin **114** and dihydroarbiglovin **118**. The synthesis of these bicarbocyclic sesquiterpenes is shown in Scheme 15 and some interesting observations were made: (i) hydrolysis of the acetate **111** caused epimerization at C-11 yielding an equimolecular mixture of isomers **113** and **114**; (ii) the allylic oxidation of (**114**) was accompanied by dehydration; (iii) stereospecific selective hydrogenation of the diene **116**.

2.7. *Epicyclocolorenone*

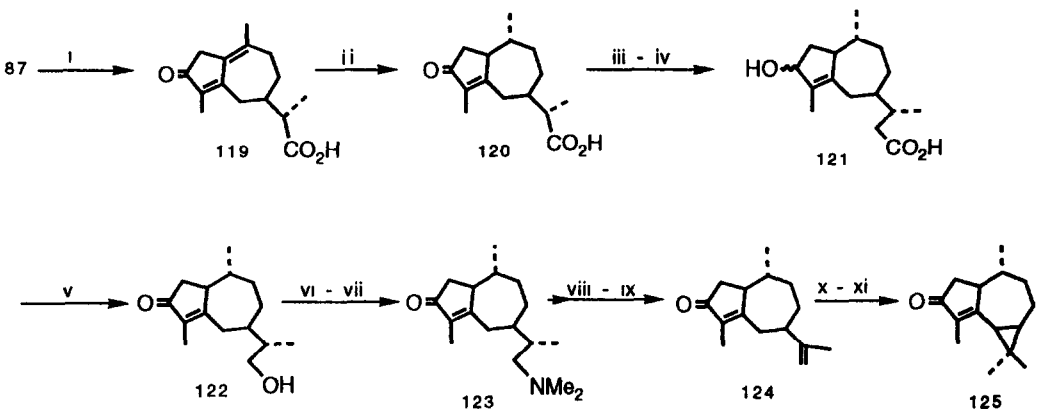
Buchi[20] developed an excellent synthesis of epicyclocolorenone **125** from the lactone **87** (Scheme 16). The transformation of lactone **87** to hydroxy enone **122** through the steps **119** → **122** was accomplished by standard organic reactions. The *p*-bromobenzene sulfonate derivative of **122** was converted to the amine ketone **123** whose N-oxide was subjected to Cope elimination to obtain the dienone **124**. The addition of HBr by base catalyzed dehydrobromination gave **125** which is the stable epimer of natural cyclocolorenone.



Scheme 14. (i) Al(*i*-PrO)$_3$, toluene, (ii) H_2, Pt/C, (iii) BzCl/Py, (iv) 50% AcOH, (v) Zn(BH$_3$)$_2$/DME, (vi) CrO_3, 2Py, CH_2Cl_2, (vii) MsCl/Py, (viii) 0.5M AcOK–AcOH, (ix) MCPBA, (x) 1M K_2CO_3 aq., MeOH, (xi) Li_2CO_3, LiBr, DMF, 118–119°C



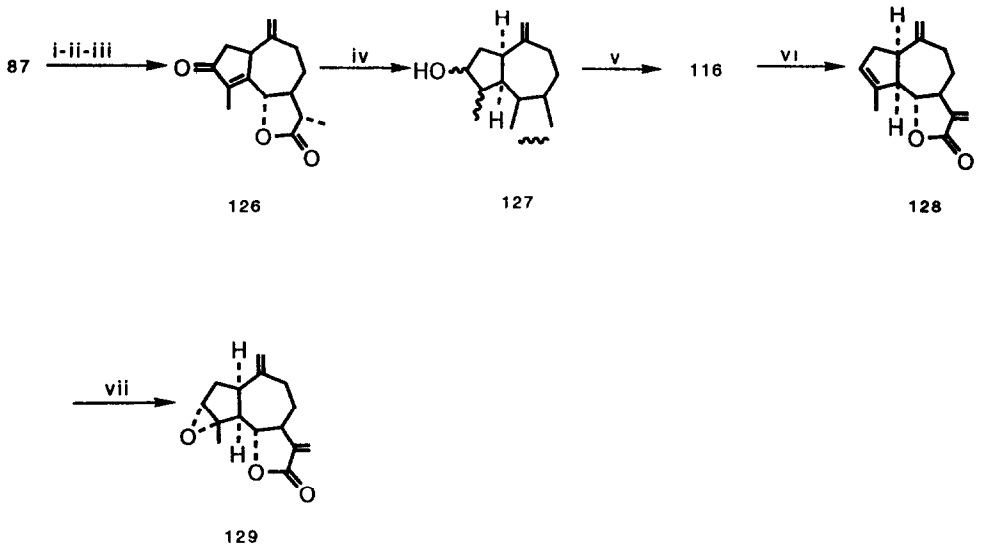
Scheme 15. (i) MsCl/Py, (ii) *t*-butyl chromate/NaOAc, (iii) *t*-BuOK/*t*-BuOH, (iv) $SOCl_2$/Py, (v) H_2, PtO_2.



Scheme 16 (i) $CrCl_2$/HOAc, (ii) H_2, Pd/C, (iii) CH_2N_2, (iv) $LiAlH_4$, (v) DDQ, (vi) *p*-$BrC_6H_4SO_2Cl$, (vii) Me_2NH, (viii) H_2O_2, (ix) Δ, (x) HBr, (xi) KOH, MeOH.

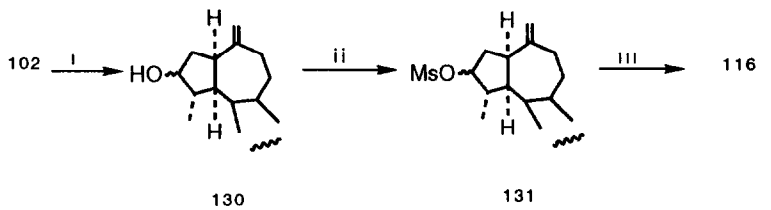
2.8. *Estafiatin*

Crabe[21] also utilized the lactone **87**, in the synthesis of estafiatin **129** (Scheme 17). The enone double bond in **126** was reduced with sodium borohydride in pyridine leaving the exocyclic double bond intact. The epoxidation of lactone **128** was stereo- and chemo-selective yielding (−)-estafiatin **129** in 51% yield along with about 10% of the β-epoxide.



Scheme 17. (i) KOH, H_2O, (ii) HCl, (iii) $SOCl_2$, (iv) $NaBH_4$, Py, H_2O, (v) HMPA, 250°C, (vi) LDA, PhSeSePh, (vii) MCPBA.

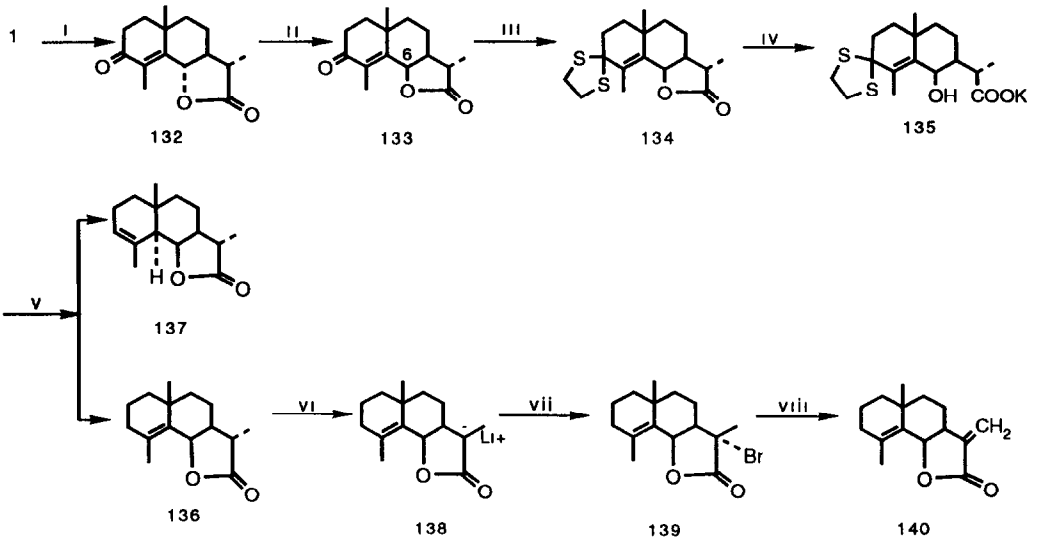
Ando[16] developed an alternative synthesis of the diene **116** as described in Scheme 18. The starting material of this work is the benzoate **102** which was readily converted to the diene **116**.



Scheme 18. (i) 1M K_2CO_3, MeOH, (ii) MsCl, Py, (iii) LiBr, Li_2CO_3, DMF.

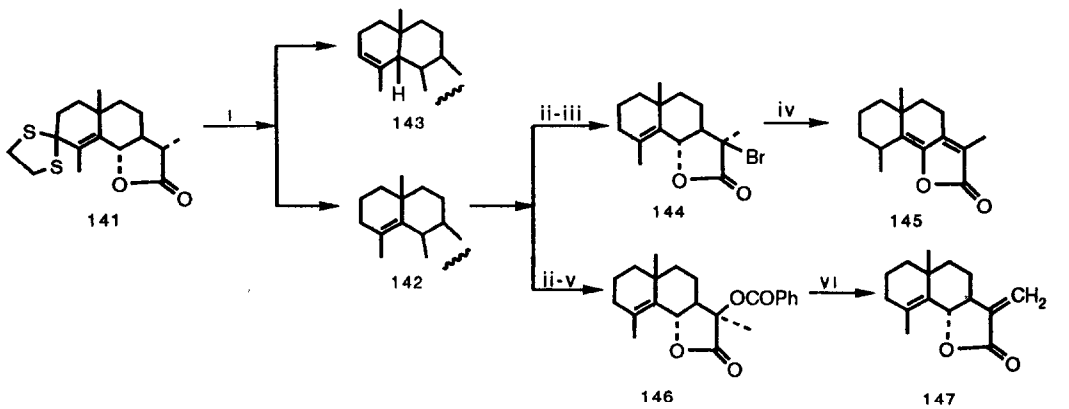
2.9. *Frullanolide and arbusculin B*

Ourisson[22] developed an interesting synthesis of two allergenic sesquiterpene lactones, frullanolide and arbusculin. The synthesis of frullanolide **140** from α-santonin is depicted in Scheme 19. Hydrogenation of α-santonin, followed by isomerization of the resulting product **132**, produced 1,2-dihydro-6-episantonin **133**. The known thioketal[23] **134**, prepared in improved yield, could not be reduced with Raney-nickel due to the formation of acidic material by hydrogenolysis of the axial alcohol C-6–O bond. The hydroxy salt **135**, however, was desulfurized to give dihydrofrullanolide **136** together with the lactone **137**. The carbanion **138** was converted to bromolactone **139** and this on dihydrohalogenation gave frullanolide **140**.



Scheme 19 (i) H_2, $RhCl(PPh_3)_3$, C_6H_6–EtOH, (ii) HCl–DMF, (iii) Excess $(CH_2SH)_2/C_6H_6$/ catalytic amount TsOH, (iv) KOH/EtOH, (v) W-2, Ra-Ni, HCl_4, (vi) Ph_3CLi, TMEDA, DME, (vii) $(CH_2Br)_2$, (viii) DBN/toluene.

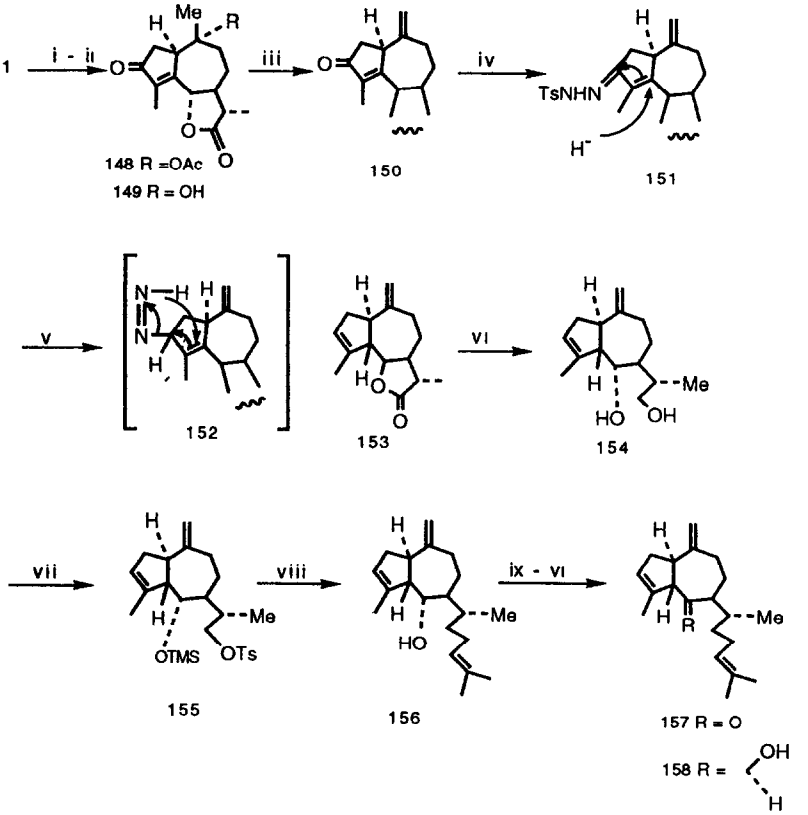
The synthesis of arbusculin B **147** from α-santonin is depicted in Scheme 20. The thioketal **141** derived from **132** underwent smooth desulfurization in contrast with the behavior of thioketal **134**. In addition to the expected 11,12-dihydro-γ-costunolide **142**, another lactone **143** was also obtained. The bromolactone **144**, whose formation is shown, could not be converted to arbusculin B **147** by the procedure described in Scheme 19, and on treatment with DBN yielded the lactone **145**. The enolate of **142** was converted to the benzoyloxy lactone **146** which was subjected to pyrolysis to give arbusculin B. The described syntheses of frullanolide and arbusculin B present much new chemistry. The difference in behavior of *cis* and *trans*-fused lactone is noteworthy.



Scheme 20 (i) W-2, Ra-Ni, EtOH, 20°C, (ii) $Ph_3C^-Li^+$, (iii) $(CH_2Br)_2$, (iv) DBN, toluene, (v) $(PhCO)_2O_2$, (vi) 450°C.

2.10. *Pachydictol and dictyolene*

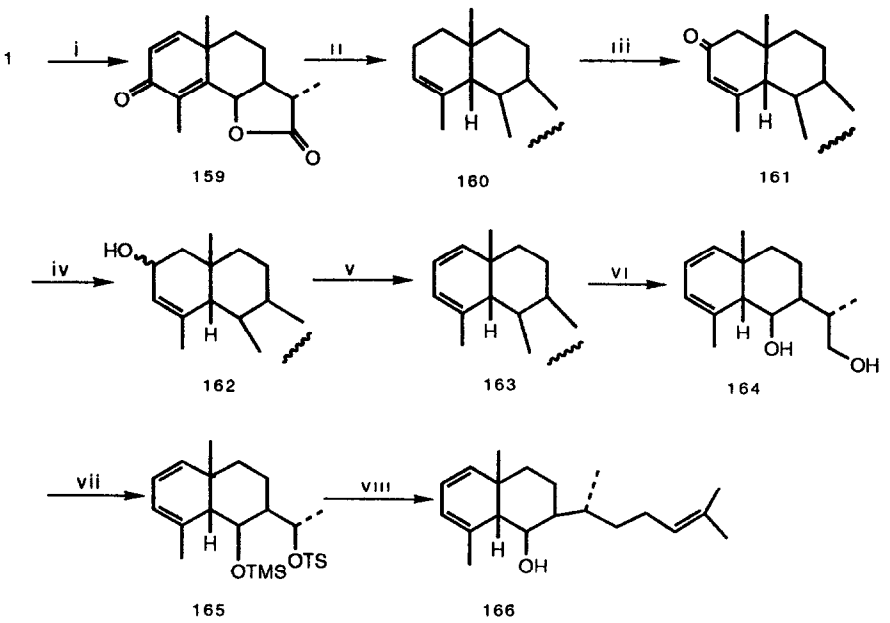
Greene[24] has developed an efficient synthesis of two marine diterpenes, (+)-pachydictol **158** and dictyolene **166** from α-santonin. Scheme 21 shows the synthesis of pachydictol **158**.



Scheme 21. (i) hν, AcOH, TO 150 Hg lamp, Ar, (ii) 5% aq. KOH, (iii) SO_2Cl_2, Py, (iv) $TsNHNH_2$, (v) catecholborane, (vi) $LiAlH_4$, Et_2O, (vii) TsCl, Py, Me_3SiCl, (viii) C_5H_9MgCl, $C_3H_7C{\equiv}CCu$, H^+, (ix) H_2CrO_4.

Photoirradiation of α-santonin by the procedure of White[25] gave O-acetylisophotosantonic lactone **148** which was converted to the known[23] dienolactone **150** by saponification and dehydration. The dehydration is highly regioselective in contrast to each of the regioselectivities in related molecules.[26] Treatment of the tosylhydrazone of **151** with catecholborane in sodium acetate gave **153**, the reduction occurring from the β-face, assuming intramolecular hydrogen transfer.[27] The stereochemical homogeneity at C-11 of the dienone lactone was verified through base catalyzed epimerization which afforded a separable mixture of **153** and its more polar epimer. The crude dienolactone **153** was converted via **154** to **155**, which was immediately subjected to copper mediated coupling with prenylmagnesium chloride to obtain 6-epipachydictol **156**. This was converted to pachydictol **158** by air oxidation and a reduction sequence of reactions.

Scheme 22 describes the synthesis[24] of dictyolene **166**. The starting material, the 6-*epi*-α-santonin **159** was obtained through the isomerization of α-santonin. Its structure was also confirmed by an independent synthesis.[28] The transformation of the ketone **161** to the diene **163** could be achieved by base treatment of the corresponding tosylhydrazone but higher yield was obtained when the ketone **161** was reduced and dehydrated. The reducing agent $NaBH_4$–$CeCl_3$ minimizes the 1,4-reduction of the enone. Neither epimerization at C-5 nor an electrocyclic process were observed in this sequence. The transformation of **163** to dictyolene **166** was realized following the procedure in Scheme 21.



Scheme 22. (i) HCl, DMF, (ii) $TsNHNH_2$, catecholborane, Na_2CO_3, NaOAc, (iii) CrO_3, 2Py, CH_2Cl_2, (iv) $NaBH_4$, $CeCl_3$, MeOH; (v) HMPA, 250°C, 15 min, (vi) $LiAlH_4$, (vii) TsCl, Me_3SiCl, Py, −40°C, (viii) C_5H_9MgCl, C_5H_7Cu, Et_2O, −25°C, H^+.

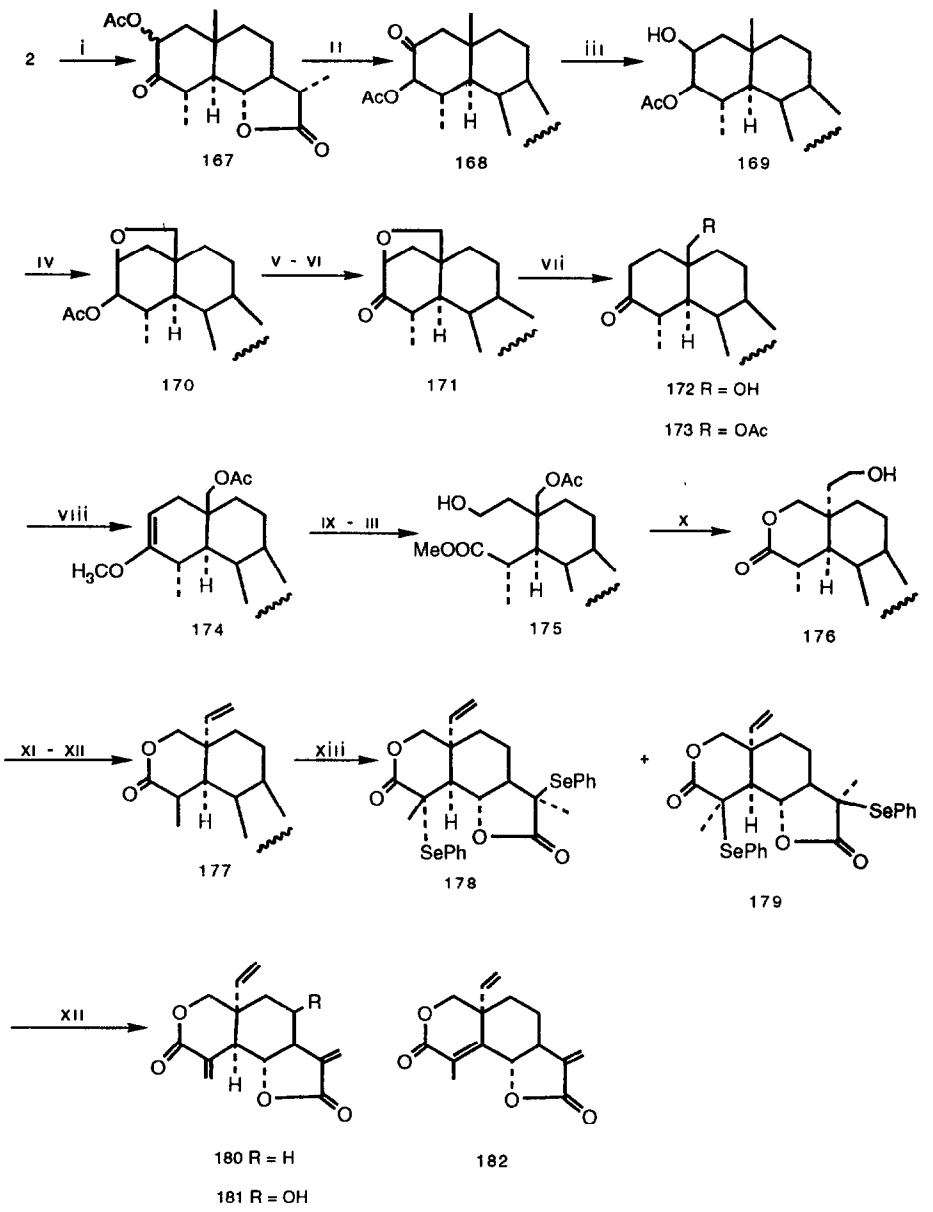
2.11. *Deoxyvernolepin*

Vernolepin **181**, an elemolide-type sesquiterpene, is noteworthy for its antitumor activity and has been synthesized by several groups.[1] Deoxyvernolepin **180** was found to be more potent than natural vernolepin againt human lymphoblastic leukemia cells in culture by Grieco.[29] Fujimoto[30] has developed a synthesis of deoxyvernolepin from α-santonin and this is shown in Scheme 23.

The acetyl derivative **167**, prepared from tetrahydrosantonin **2**, on treatment with tetramethylammonium acetate underwent 1,2 carbonyl transposition affording the ketoacetate **168** which was readily converted to the ketoether **171**. The furan ring was cleaved by heating with zinc iodide and zinc powder in acetic acid to give a mixture of **172** (58%) and **173** (26%). Conversion to the enol ether **174** and ozonolysis and reduction gave the ester **175** which could be lactonized to **176**. Olefination reaction via the selenide was followed by the formation of the bis selenides **178** and **179** via bisenolate of **177**. Oxidation of each of the separate selenides gave deoxyvernolepin **180** but in contrasting yields. The *cis*-selenide **179** was transformed in 80% yield whereas the *trans*-selenide **178** in only 2% yield, next forming the isomer **182** (62%).

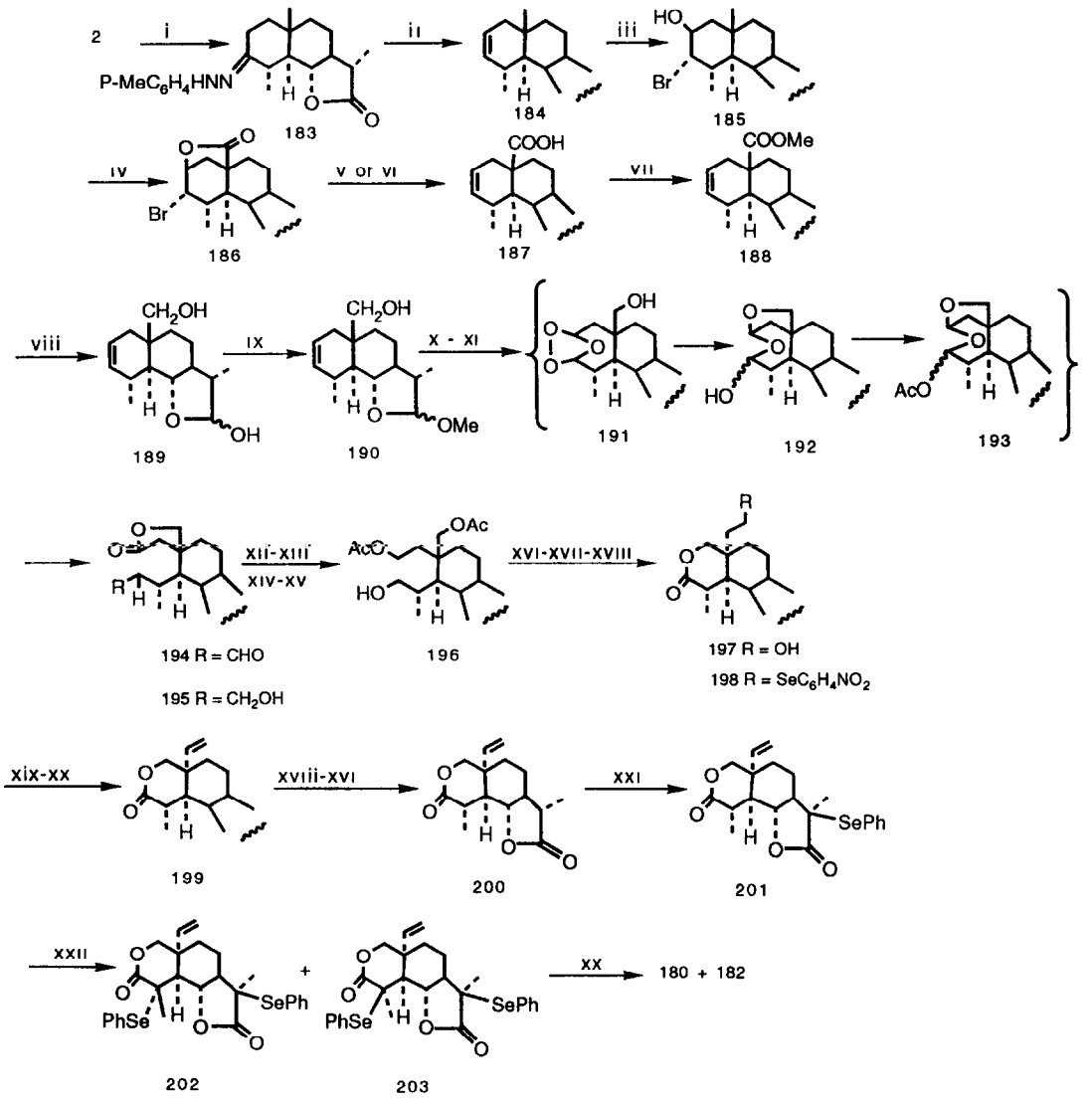
Another interesting synthesis of deoxyvernolepin **180** by Watanabe and Yoshikoshi[32,33] is shown in Scheme 24. The tosylhydrazone **183** was converted to the olefin **184** regioselectively and treatment of this with NBS in aqueous DMSO gave the bromohydrin **185**. Irradiation of **185** gave the bromolactone **186** which on reductive cleavage gave the acid **187**. Esterification gave the ester **188**, available in 40–50% yield from **25** without purification of the intermediates.

Reduction of **188** gave the lactol **189** which was methylated to give **190** and this, on oxidation with a slight excess of ozone followed by treatment with Ac_2O/Py at room temperature, unexpectedly provided the formyl lactone **194** presumably via the products **191** → **193**. The ozonization followed by reduction with DMSO gave a mixture of products. The alcohol **195** was converted to the lactone **197** via **196** by a series of standard reactions. The selenide **198** derived from **197** was oxidized to obtain **199**. Hydrolysis of the lactol and Jones oxidation gave the lactone **200**, also available in very



Scheme 23 (i) $Pb(OAc)_4$–BF_3, (ii) Me_4NOAc–glyme, (iii) $NaBH_4$, (iv) HgO–I_2, (v) 5% KOH–MeOH; (vi) PCC–CH_2Cl_2, (vii) Zn–ZnI, (viii) $HC(OMe)_3$–PPTS, (ix) O_3, (x) MeOH–10% HCl, (xi) O-NO_2-C_6H_4SeCN, Bu_3P, (xii) 30% H_2O_2, THF, (xiii) LDA, PhSeCl, THF, HMPA

poor yield by direct oxidation of **199**. It is worth mentioning that this process altered the orientation of the methyl group. On selenenylation it fortunately gave monoselenide **201** and this on sulphenylation gave **202** in major proportion and **203** in minor proportion. On oxidation, **202** gave the desired deoxyvernolepin **180** and its regioisomer **182** in a ratio or 1 : 3 whereas the minor isomer **203** only gave deoxyvernolepin **180**. The oxidative elimination of the phenylsulphonyl group proceeded at an unusually low temperature and the product ratio was helpful in assigning the stereochemistry of sulphenylation products **202** and **203**.

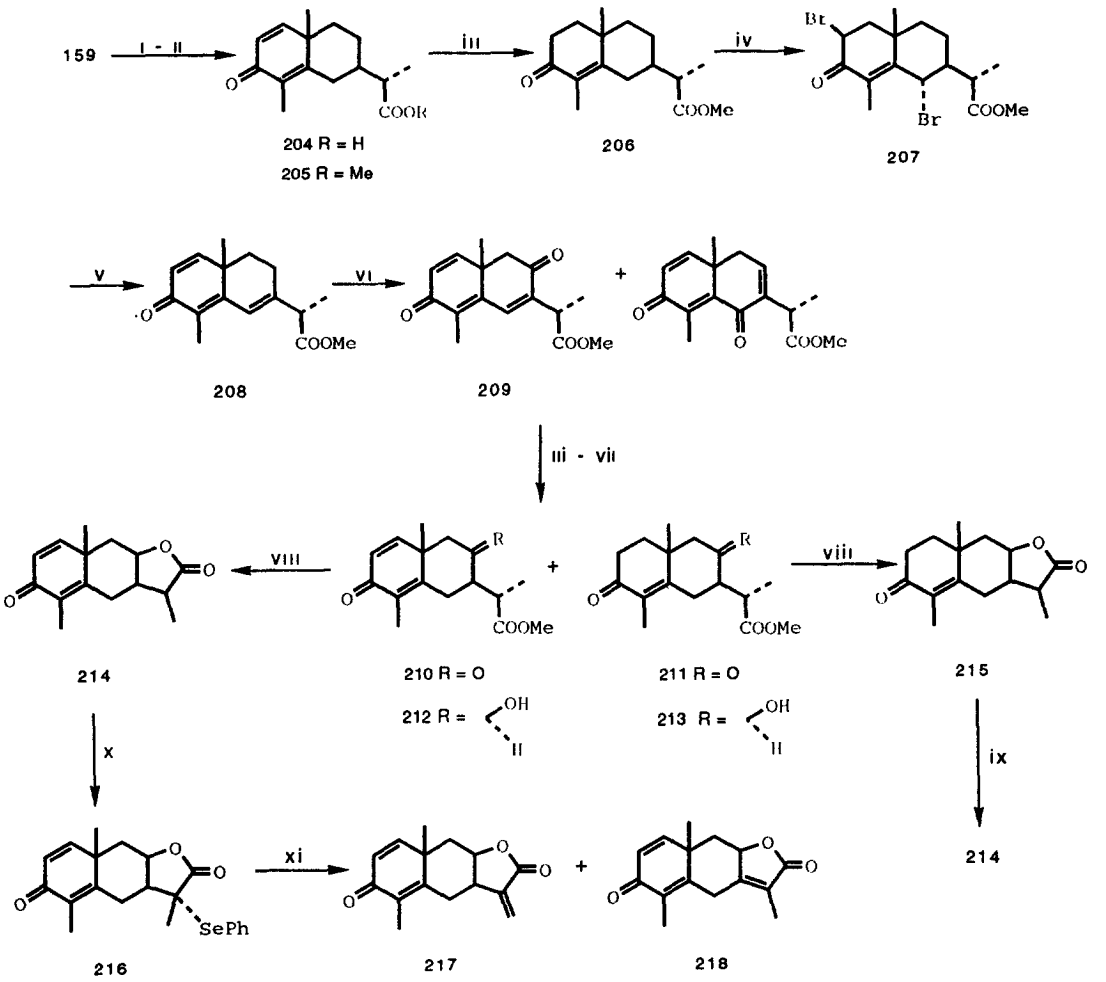


Scheme 24. (i) *p*-$MeC_6H_4SO_2MHNH_2$, MeOH, (ii) *i*-Pr_2NLi, THF, (iii) NBS, aq. Me_2SO, (iv) $Pb(OAc)_4$, I_2, hν, cyclohexane, (v) Zn–Ag, EtOH, (vi) Zn, HOAc, (vii) CH_2N_2, (viii) *i*-Bu_2AlH, toluene, (ix) $CH(OMe)_3$/TsOH, (x) O_3, (xi) Ac_2O/Py, (xii) DHP, (xiii) $LiAlH_4$, (xiv) Ac_2O/Py, (xv) PPTS, (xvi) Jones Reagent, (xvii) 0.5 M aq. NaOH, (xviii) 6 M aq. HCl, (xix) O-$NO_2C_6H_4SeCN$, Bu_3P, (xx) 30% H_2O_2, (xxi) *i*-Pr_2NLi, PhSeSePh, (xxii) *i*-Pr_2NLi, Ph_2S_2.

2.12. *Yomogin, telekin and pinnatifidin*

α-Santonin was utilized by Japanese chemists for the synthesis of sesquiterpene α-methylene-γ-lactones such as yomogin[33] **217**, telekin[33] **225** and pinnatifidin[34] **235**. Scheme 25 describes the transformation of α-santonin into yomogin **217**.

The ketoester **206** had previously been synthesized[35] by direct reduction of α-santonin with lithium in liquid ammonia followed by direct esterification with diazomethane but this method is exceptionally laborious on a large scale. The bromination and dehydrobromination sequence on the ketoester **206** gave an excellent yield of the dienone **208** (91%). Direct hydrogenation with a variety



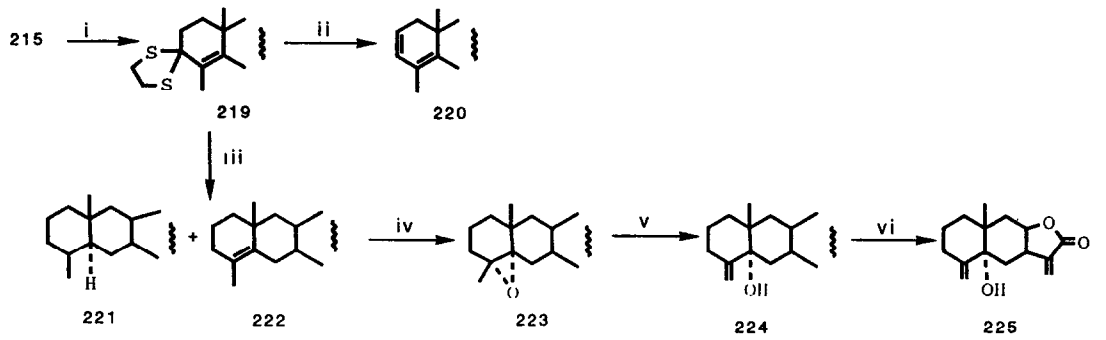
Scheme 25. (I) MeOH, AcOH, Zn dust, (II) CH_2N_2, (III) $(Ph_3P)_3RhCl$, (IV) Br_2, CH_2Cl_2, (V) Li_2CO_3, LiBr, DMF, (VI) $C_4H_9Cr_2O_7$, (VII) $NaBH_4$, MeOH, $-20°C$, (VIII) NaOH (aq.), HCl, (IX) DDQ, (X) PhSeSePh, (XI) H_2O_2, AcOH, THF.

of reagents was unsuccessful. Oxidation of the dienone **208** with $C_4H_9Cr_2O_7$ gave principally **209** (28–39%) while other oxidizing agents (chromium trioxide, selenium dioxide) were unsatisfactory. During the transformation of the dienone **209** to lactone **214**, it was observed that the presence of C(6),7-double bond caused difficulty in the lactonization and it was therefore removed by catalytic reduction. Phenylselenylation of **214** followed by oxidation of the resulting product yielded yomogin **217** and an endocyclic isomer **218** in a ratio of 1.2 : 1.

The conversion of α-santonin into telekin **225** is shown in Scheme 26.

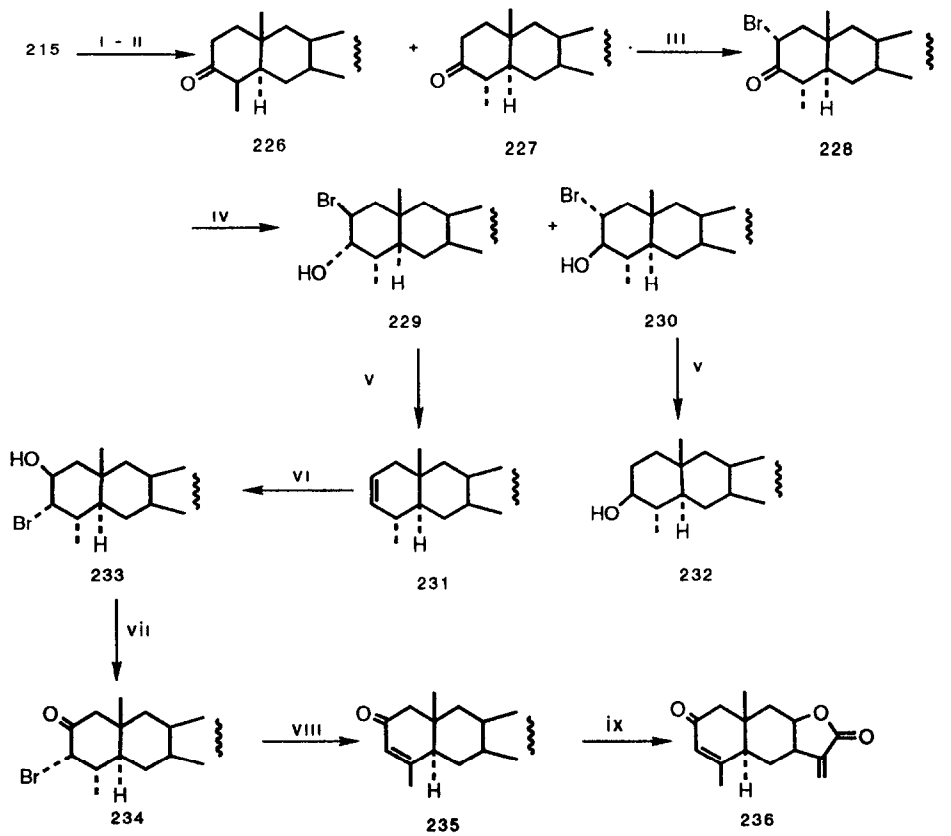
Desulfurization of the thioketal **219** with Raney-nickel in ethanol gave a mixture of product **221** and **222**, whereas Raney-nickel in acetone gave the diene **220**. Epoxidation of the mixture of **221** and **222** gave epoxide **223** which was reduced with lithium diethylamide to allylic alcohol **224** (57%). Reduction with lithium diisopropylamide in tetrahydrofuran gave **224** only in low yield (11%). The conversion of the allylic alcohol **224** to telekin **225** was accomplished by the procedure as described in the synthesis of yomogin.

The synthesis of another sesquiterpene lactone, pinnatifidin **235** from α-santonin, is described[34]



Scheme 26. (i) $(CH_2SH)_2$, $BF_3 \cdot Et_2O$, (ii) W-2 Ra-Ni, Me_2CO, (iii) W-2 Ra-Ni, EtOH (iv) MCPBA, (v) $LiEt_2N$, Et_2O, (vi) PhSeSePh, H_2O_2, AcOH, THF

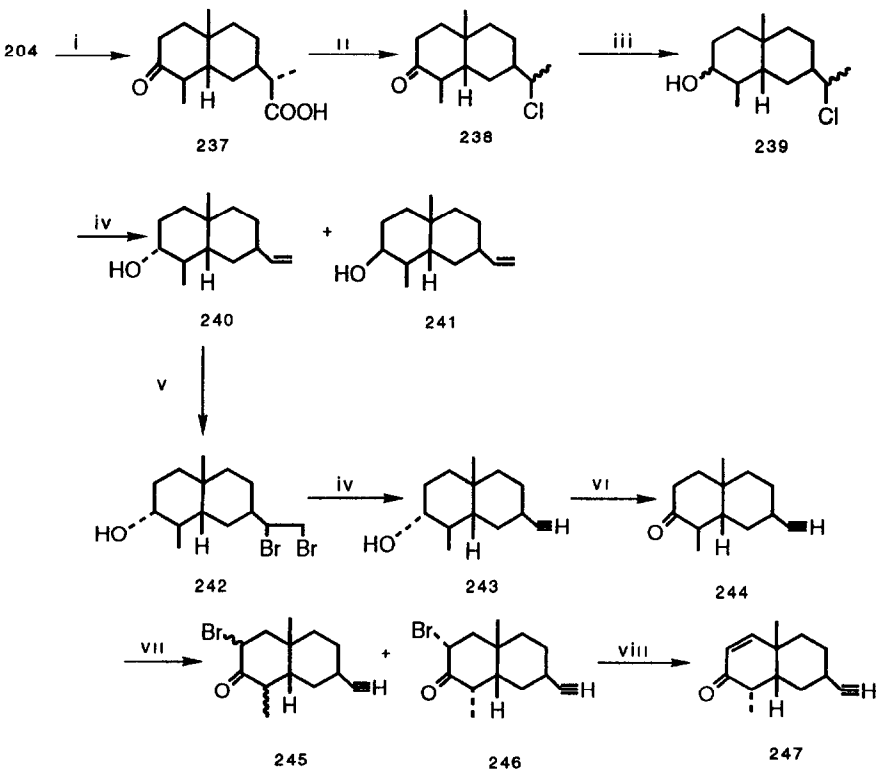
in Scheme 27. The lactone **215** on hydrogenation yielded a mixture of saturated lactones **226** and **227** which were isomerized with acid to obtain **227** in good yield. Bromination of **227** followed by metal hydride reduction afforded a mixture of bromohydrins **229** and **230**. On reduction with zinc in acetic acid the bromohydrin **229** gave olefin **231** whereas the bromohydrin **230** gave **231** together with alcohol **232**. The olefin **231** was converted to the α,β-unsaturated ketone **235** whose conversion to pinnatifidin **236** was carried out by the procedure already described.



Scheme 27. (i) Pd/C, H, (ii) H^+, (iii) Br_2, (iv) $NaBH_4$, (v) Zn dust, AcOH, (vi) NBS, DMSO, (vii) Jones Reagent, (viii) DBU, (ix) PhSeSePh, H_2O_2, AcOH, THF.

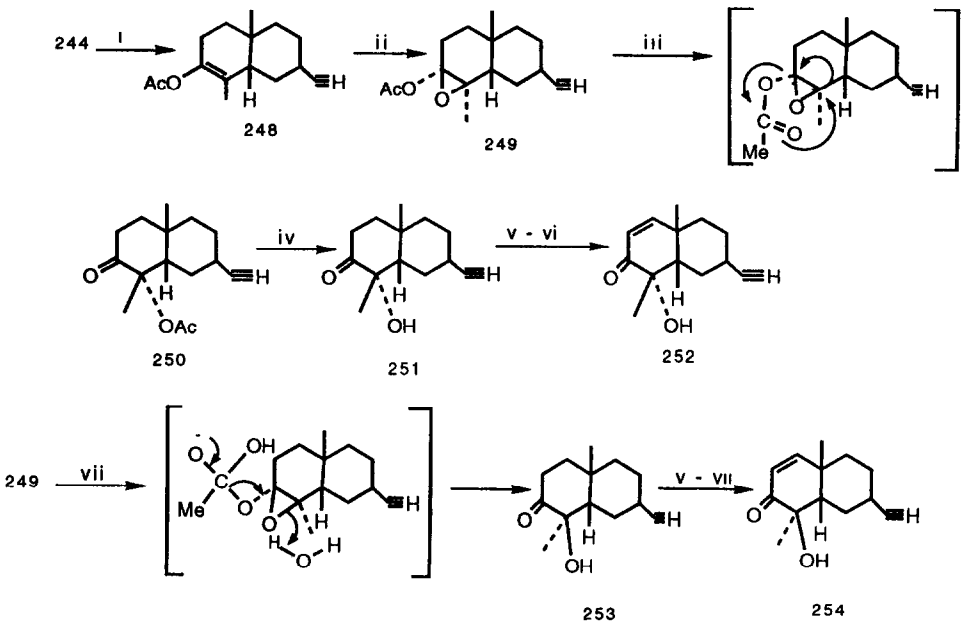
2.13. *Chamaecyone*

α-Santonin was also utilized for the synthesis[36] of nor-sesquiterpene chamaecyone **247** as shown in Scheme 28. The hydrogenation of **204** in the presence of base afforded saturated ketone **237** with the most stable configuration at C-4. The ketone **237** was subjected to chlorodecarboxylation following the Kochi's modification of the Hunsdiecker reaction to give **238** as a mixture of diastereoisomers. The ketone **238** was reduced and treated with base to achieve dehydrochlorination. A mixture of alcohols **240** and **241** was obtained and these were separated. The transformation of **240** into acetylenic ketone **244** was accomplished by bromination and dehydrobromination followed by oxidation. The ketone **244** on bromination gave a 1:1 mixture of bromides **245** and **246**. Dehydrobromination of **245** yielded the natural chamaecyone **247**. Epimerization at C-4 has been observed in the formation of **246** during bromination. Epimerization of the β-methyl to the more stable α-configuration has been observed at C-2 of the *trans*-decalone[4,38,40] but this is the first example of a *cis*-decalone.



Scheme 28. (i) 5% Pd–C, EtOH, 1% KOH, (ii) LiCl and $Pb(OAc)_4$, (iii) $NaBH_4$, MeOH, (iv) C_4H_9OK, C_4H_9OH, (v) Br_2 in CCl_4, (vi) $CrO_3 \cdot 2Py$, (vii) Br_2 in AcOH, (viii) LiBr, Li_2CO_3, DMF

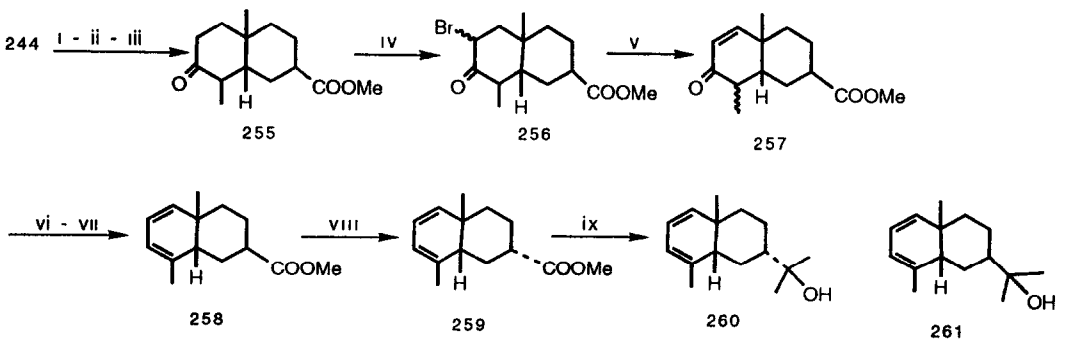
The same group of workers also utilized[37] α-santonin for the synthesis of 4β-hydroxychamaecyone **254** and its C-4 epimer with the object of establishing the structure of 'hydroxyisochamaecyone' which is the acetylenic nor-sesquiterpene alcohol. Scheme 29 illustrates the route. One of the most interesting aspects of this synthesis is the pyrolytic rearrangement as well as the basic hydrolysis of the oxide **249**. Pyrolytic rearrangement of **249** gave the ketoacetate **250** which on hydrolysis yielded **251**. Bromination and dehydrobromination of **251** gave natural 4α-hydroxychamaecyone **252**. Alkaline hydrolysis of enolacetate **249** gave the 4β-hydroxy compound **253** which was converted to β-hydroxychamaecyone **254**.



Scheme 29 (i) $C_4H_8O_2$, H^+, (ii) MCPBA, (iii) 180°C, (iv) KOH/EtOH, (v) Br_2/AcOH, (vi) LiBr, Li_2CO_3, DMF, (vii) Alkaline hydrolysis.

2.14. *Occidentalol and its C-7 epimer*

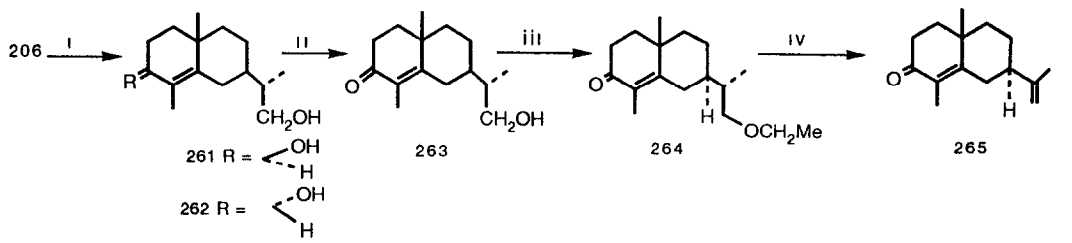
Japanese chemists have reported[38] the transformation of α-santonin into occidentalol **260** and its C-7 epimer **261** as shown in Scheme 30. The ketone **244** was converted to the ester **255** which gave the monobromide **256** whose transformation to a single diene **258** was achieved via the α,β-unsaturated ketone **257**. This indicated that the ketone **257** was epimeric at C-4, not at C-7. The epimerization at C-7 of **258** was effected by treatment with potassium *t*-butoxide in *t*-butanol followed by hydrolysis of the resulting *t*-butyl ester and subsequent methylation. This operation afforded at 22 : 1 mixture of the diene **259** and **258**. The diene **259** afforded the occidentalol **260** on treatment with methylmagnesium bromide. On similar treatment, **258** gave the C-7 epimer **261** of occidentalol.



Scheme 30. (i) $NaIO_4$–OsO_4, (ii) Ag_2O, (iii) CH_2N_2, (iv) Br_2/AcOH, (v) LiBr. Li_2CO_3, DMF, (vi) $NaBH_4$, (vii) Al_2O_3, 4% Pyr, (viii) 1N C_4H_9OK/C_4H_9OH, aq. alkali, CH_2N_2, (ix) MeMgBr.

2.15. *α-Cyperone*

Piers and Cheng[39] have reported an interesting synthesis of α-cyperone **265** from α-santonin as outlined in Scheme 31. Reduction of the ketoester **206** gave a mixture of alcohols **261** and **262** which on oxidation was converted into the ketoalcohol **263**. It was necessary to have carefully selected conditions in order to oxidize the allylic alcohol without affecting the primary alcohol group. Conversion of the ketoalcohol **263** to the methyl carbonate **264**, followed by pyrolysis afforded the cyperone **265** in 84% yield.

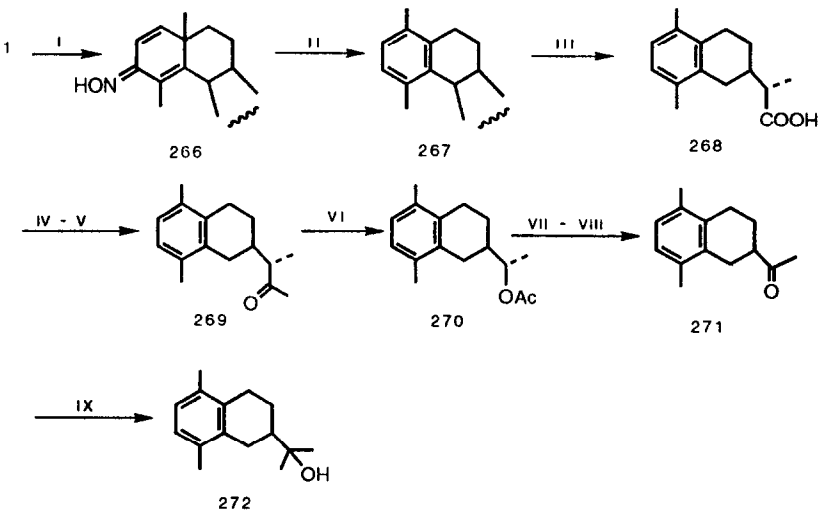


Scheme 31. (i) $LiAlH_4$, Et_2O, (ii) DDQ, Dioxane, (iii) $ClCO_2Me$, Py, (iv) 400°C.

Treatment of the ketoalcohol **263** with methyl chloroformate followed by pyrolysis afforded α-cyperone **265** in 61% yield together with the ketoalcohol **263** (32%). The present route to α-cyperone **265** (overall yield 20%) is superior to that previously reported[40] (4%). This synthetic route could be used for the preparation of pure α-cyperone **265** on a moderately large scale.

2.16. *Occidol*

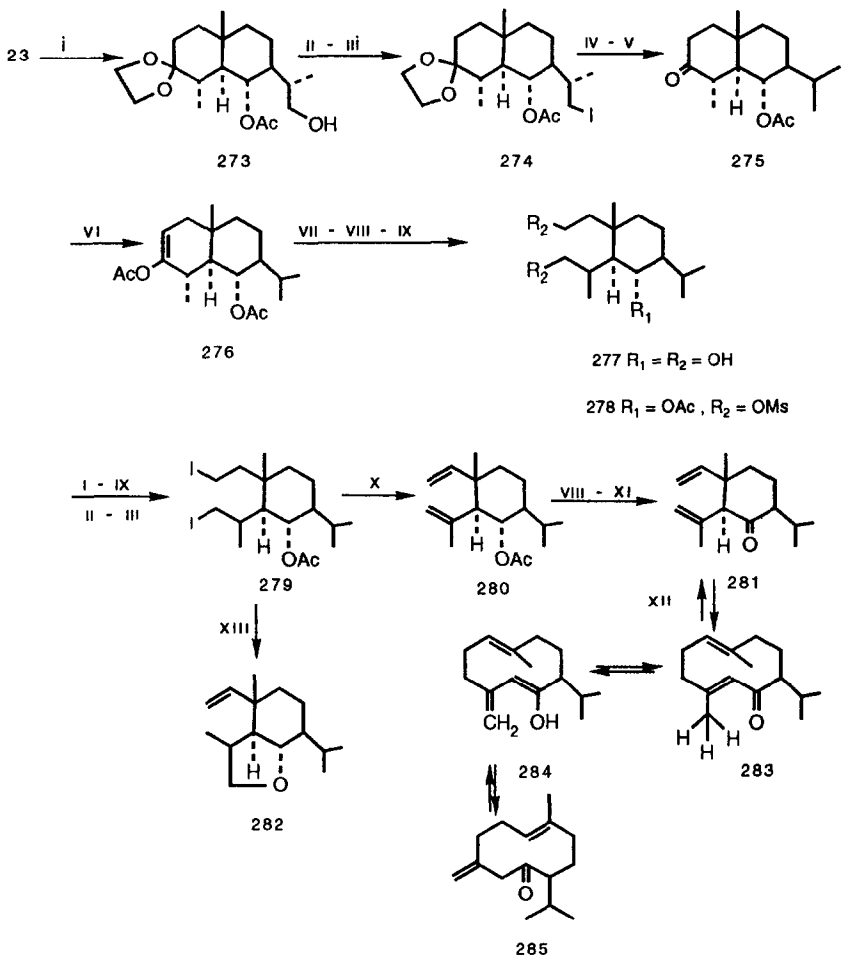
The synthesis of the sesquiterpene alcohol occidol **272** was achieved[41] from α-santonin as shown in Scheme 32. The oxime **266** was reduced to hyposantonin **267** which was reductively cleaved to hyposantonus acid **268**, which was then converted via the acid chloride to the methyl ketone **269**. Baeyer–Villiger oxidation of **269** produced an acetate **270** which was then hydrolyzed and oxidized to obtain the ketone **271** and this, on treatment with methylmagnesium iodide, gave occidol **272**.



Scheme 32. (i) NH_2OH, (ii) Na–Hg, (iii) Zn/HOAc, (iv) $SOCl_2$, (v) Me_2Cd, (vi) MCPBA, (vii) KOH, (viii) CrO_3, Py, (ix) MeMgI.

2.17. *Shyobunone*

The synthesis of shyobunone **281** from α-santonin was achieved[42] by Japanese investigators and is outlined in Scheme 33. The diol **23** was converted to the iodoacetate **274** via the acetate **273** and its methyl derivative.[43,44] Reduction of **274** followed by deketalization gave the ketoacetate **275**. The degradation of ring A of ketoacetate **275** was carried out by a route different from that used by Ando.[13] The enolacetate **276** was subjected to ozonization followed by reduction to give the triol **277** which was converted by straightforward steps into diiodide **279**. Dehydrohalogenation of **279** with DBU gave the diene **280** in excellent yield whose transformation to shyobunone **281** was accomplished by reduction and oxidation. Dehydrohalogenation of **279** with potassium-*t*-butoxide gave an ether **282** in high yield.

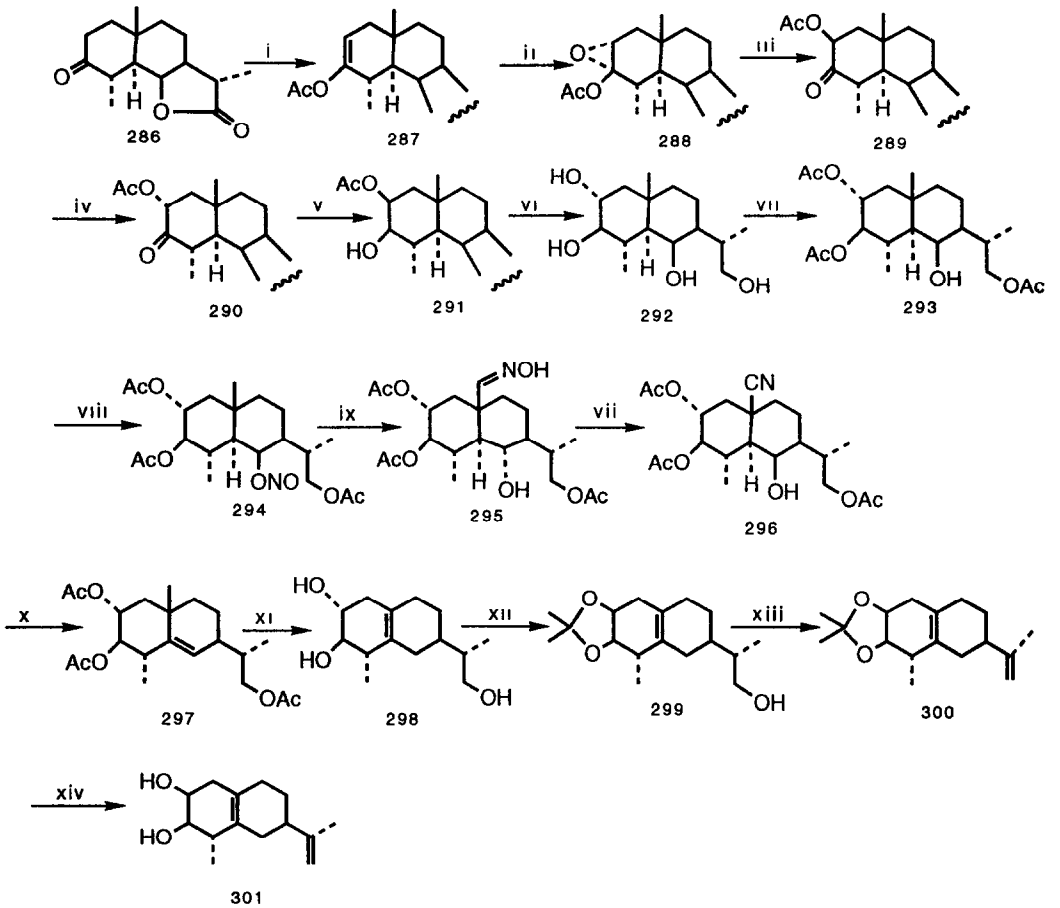


Scheme 33. (i) Ac_2O/Py, (ii) MsCl/Py, (iii) NaI/Me_2CO, (iv) $NaBH_4$/DMSO, (v) AcOH, (vi) $C_5H_8O_2$, H^+, (vii) O_3, (viii) $LiAlH_4$, (ix) 5% MeOH–KOH, r t., (x) DBU, (xi) Jones Reagent, (xii) 160°C, (xiii) *t*-BuOK

Shyobunone **281** was converted into preisocalamendiol **285** (30%) on heating in a sealed tube and this is the first example of the synthesis of a naturally occurring germacrane-type sesquiterpene. This transformation is noteworthy because the divinylcyclohexane unit of shyobunone **281** is expected to be more stable than the 1,5-cyclodecadiene unit of **285**. In this case, however, the equilibrium is shifted to 1,5-hydrogen shift in the enolization of **283** to **284**.

2.18. *Rishitin*

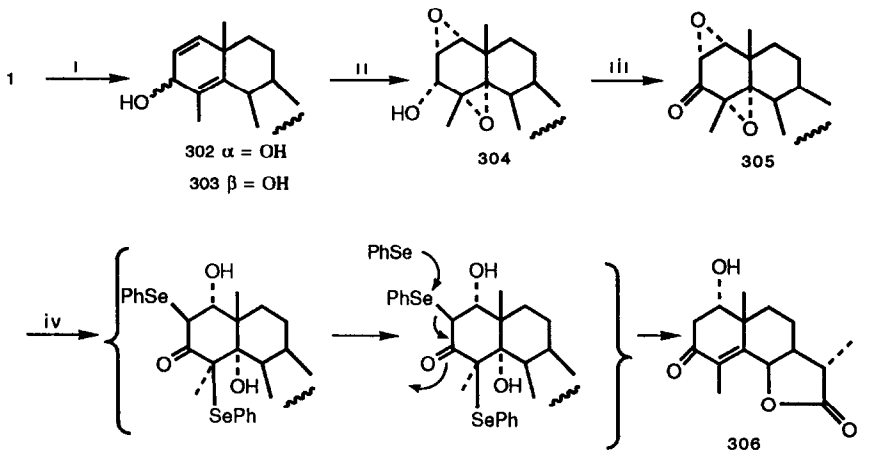
Masamune and coworkers[45] accomplished the synthesis of antifungal norsesquiterpene rishitin **301** from α-santonin as shown in Scheme 34. The tetrahydrosantonin **286**, prepared by the procedure,[39] was converted into hydroxyacetate **293** in quantitative yield. Removal of the angular methyl group with the introduction of C_9–C_{10} double bond was carried out by the modified Barton reaction **294** → **295** followed by decyanation of the allyl nitrile **297**. The acetonide **299** was converted to **300** by tosylation, iodination and hydrolysis. Acidification of **300** afforded rishitin **301** (2.9% from α-santonin). The synthesis is long but has been achieved with good stereocontrol.



Scheme 34 (i) $C_5H_8O_2/H^+$, (ii) $C_8H_6O_5/CHCl_3$, (iii) 170°C, (iv) HBr in AcOH, (v) $NaBH_4$ in MeOH, 0°C, (vi) $LiAlH_4$/THF, (vii) Ac_2O/Py, (viii) NOCl/Py, (ix) 200 Watt Hanovia high pressure Hg lamp, (x) MsCl/Py, (xi) Na, toluene, EtOH, (xii) Me_2CO, silica gel (Wakogel Q-23), (xiii) TsCl/Py, NaI/Me_2CO, (xiv) H_2O^+

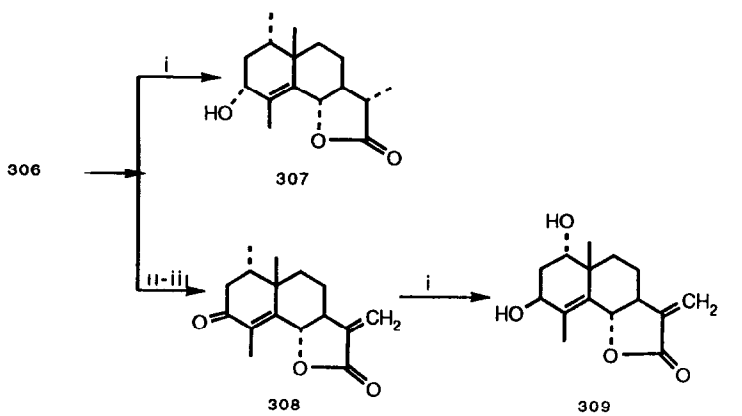
2.19. *Dehydroisoerivanin, isoerivanin, ludovicin C and* 1α,3α*-dihydroxyarbusculin B*

In 1987 Yoshikoshi[46] and collaborators reported the first synthesis of the santanolides dehydroisoerivanin **306**, isoerivanin **307**, ludovicin C **308** and 1α,3α-dihydroxyarbusculin B **309** from α-santonin by employing the organoselenium mediated reduction of α-epoxy ketone[47] (Scheme 35). Reduction of α-santonin with sodium borohydride–cerium chloride gave a 3:1 mixture of the alcohols **302** and **303** in 97% yield. Many other reducing agents have been found to be ineffective.



Scheme 35. (i) $NaBH_4$–$CeCl_3$, MeOH, (ii) MCPBA, CH_2Cl_2, (iii) CrO_3, 2Py, CH_2Cl_2, (iv) Na^+ |$PhSeB(OEt)_3$|, AcOH, EtOH.

Epoxidation of the mixture of alcohols gave 65% yield of the epoxide **304**. Due to the directing effect of the hydroxyl group, α-epoxidation of the tetrasubstituted C_4–C_5 was followed by the epoxidation of C_1–C_2. Oxidation at C_1–C_2 was not observed unless a large excess of *m*-chloroperbenzoic acid was employed owing to the steric repulsion of the angular methyl group. The ketone **305** on treatment with sodium benzeneselenolate yielded the dehydroisoerivanin **306**, probably by the mechanism shown in Scheme 35. Reduction of dehydroisoerivanin **306** gave isoerivanin **307** (Scheme 36). The transformation of **306** into ludovicin **308** followed by previously described procedures and the reduction of ludovicin **308** gave 1,3-dihydroxyarbusculin B **309**.

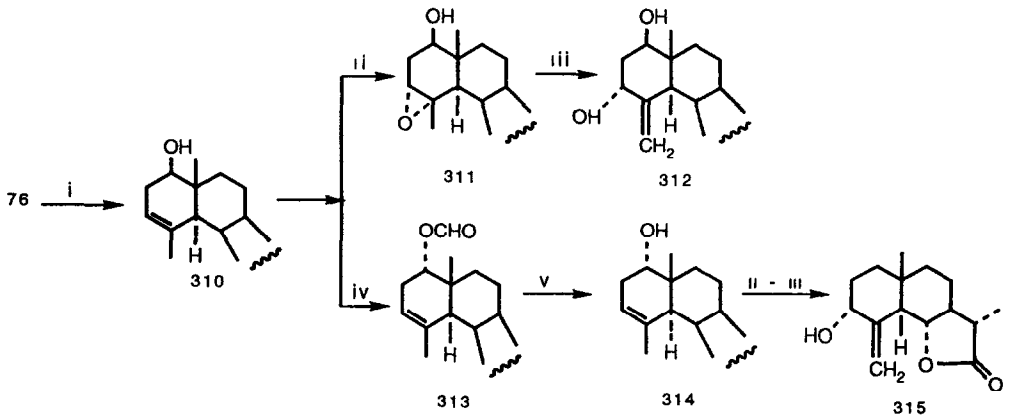


Scheme 36. (i) $NaBH_4$–$CeCl_3$, MeOH, (ii) LDA/THF, PhSeSePh, (iii) H_2O_2, AcOH THF.

2.20 *Erivanin and 1-epierivanin*

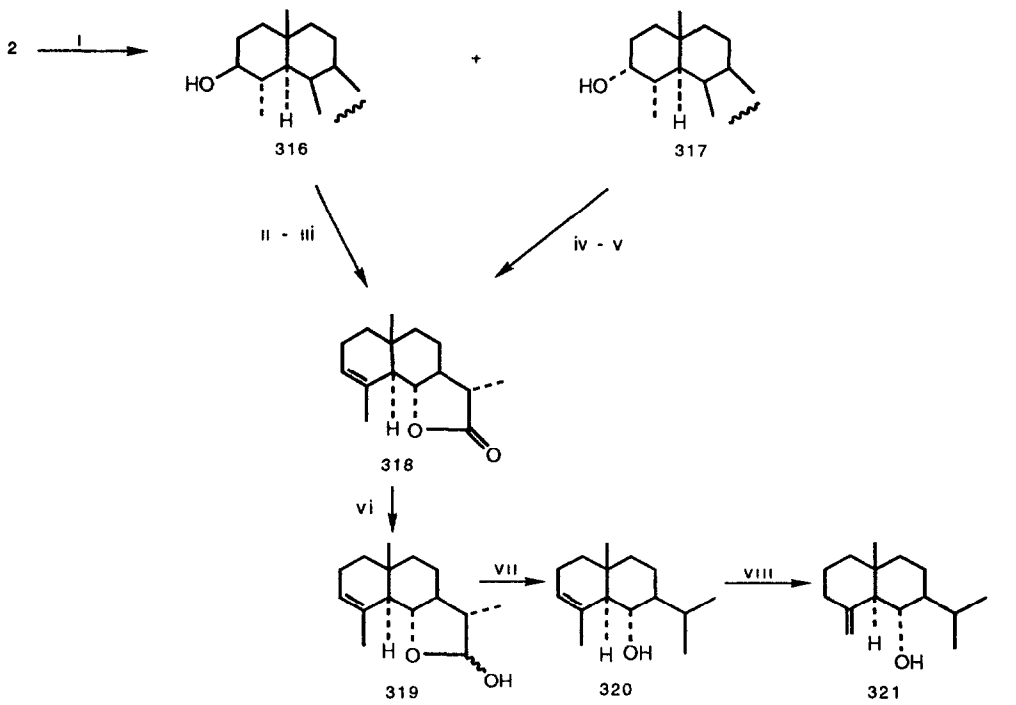
Harapanhalli[48] has reported the first synthesis of erivanin **315** and 1-epierivanin **312** from α-santonin (Scheme 37). The enone **76** on reduction afforded the β-alcohol **310** as the sole product. Epoxidation on the alcohol gave the α-epoxide **311** and this clearly indicates that the β-hydroxyl group did not exert any directing influence in the epoxidation of the homoallylic alcohol. This observation agrees very nicely with the generalization of Berti[49] that a homoallylic hydroxyl group

can direct epoxidation only if it is sufficiently near to the double bond. On treatment with bulky bases the epoxide **311** underwent rearrangement to 1-epierivanin **312**.



Scheme 37 (i) $NaBH_4$, 0°C, (ii) MCPBA, (iii) LDA or $Al(i\text{-}PrO)_3$, (iv) diethyl azodicarboxylate (DEAD), Ph_3P, HCOOH in THF, (v) aq. MeOH, a few drops HCl

In order to achieve the synthesis of erivanin **315**, it was necessary to epimerize the β-alcohol group of epoxide **311** to the α-epimer and this was achieved effectively by the procedure reported by Mitsunobu.[50,51] Treatment of the epoxide **311** with Mitsunobu's reagent gave the formate **313** which on careful hydrolysis afforded the inverted alcohol **314**. This alcohol gave erivanin **315** using



Scheme 38. (i) $NaBH_4$ $LiAl(O\text{-}t\text{-}Bu)_3$, (ii) SO_2Cl/Py, (iii) LiBr, Li_2CO_3, DMF, (iv) $MsCl/Py$, (v) Li_2CO_3, (vi) DIBAL, (vii) N_2H_4, KOH, (viii) hν

the sequence reported for the β-isomer of 1-epierivanin **312**. A number of reagents were tried but none of them was found satisfactory.

2.21. *Junenol and iso-junenol*

An interesting synthesis[52] of junenol **321** and iso-junenol **320** was developed from α-santonin as shown in Scheme 38. α-Tetrahydrosantonin **2** on reduction gave a mixture of alcohols **316** and **317** in a ratio of 5:1. Dehydration of these alcohols in acid medium using *p*-TsOH in toluene, or by treatment with $SOCl_2$–pyridine, was not successful. The chloro derivative of the alcohol **316**, prepared by treatment with $SOCl_2$–pyridine, was purified and subjected to dehydrohalogenation with LiBr–Li_2CO_3 and DMF to obtain the alkene **318**. This alkene was also obtained in lower selectivity by elimination of the mesylate of the alcohol **316**. Reduction of the alkene gave the lactol **319** whose conversion to iso-junenol **320** was effected by the application of the Huang–Minlon method. Irradiation of iso-junenol **320** led to the formation of junenol **321**. This synthesis of junenol **321** from α-santonin involved only 7 steps with an overall yield higher than reported earlier.[53]

3. CONCLUSIONS

α-Santonin has been transferred into various terpenoid compounds by many paths, indicating its utility in natural product chemistry. It has been shown that germane class sesquiterpenes such as costunolide and dihydrocostunolide, sesquiterpene lactones such as vulgarin, saussurea lactone, frullanolide and arbusculin B, α-methylene-γ-lactones such as yomogin, telekin, pinnatifidin and tuberiferine, marine diterpenes such as pachydictol and dictyolene, elemolide sesquiterpenes such as vernolepin and deoxyvernolepin, norsesquiterpene chamaecyone, sesquiterpene alcohols such as occidentalol and occidol, and antifungal sesquiterpenes like rishitin, have been synthesized from α-santonin.

A variety of synthetic reactions has been used in these transformations. For example, the construction of the α-methylene-γ-lactone unit was achieved by Grieco's procedure of selenylation followed by oxidation. The construction of the cyclodecane unit was realized by Corey and Fujimoto using a photochemical reaction. An interesting application of the modified Barton reaction was applied to remove the angular methyl group in the synthesis of rishitin. The successful application of the Mitsunobu epimerisation procedure was observed in the synthesis of erivanin. The organo-selenium mediated reduction of epoxy ketones was utilized in the synthesis of santonolides. The cleavage of epoxy mesylate with aluminium isopropoxide in refluxing toluene was found useful in the synthesis of saussurea lactone.

One can expect that in the future α-santonin will be used as a precursor to many other natural products.

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REFERENCES

1. Heathcock, C. H. In *Total Synthesis of Natural Products*, Vol. 2, ApSimon, J. W. (Ed), Wiley, New York 1973, pp. 315–324 and Vol. 5, p. 150.
2. Grieco, P. A.; Nishizawa, N. M *J. Org Chem.* **1977,** *42*, 1717.
3. Fischer, N. H.; Mabry, T J. *Chem. Commun.* **1967,** 1235.
4. Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1965,** *87*, 5736.
5 Fujimoto, Y.; Shimizu, T., Ohmori, M ; Tatsunoi, T. *Chem. Pharm. Bull.* **1979,** *27*, 923.
6 Simonovic, D. M.; Rao, A. S.; Bhattacharya, S. C., *Tetrahedron* **1967,** *23*, 1267.
7. Ando, M.; Akahane, A., Takase, K. *Bull. Chem. Soc. Japan* **1978,** *51*, 284

8. Ando, M.; Tajıma, K.; Takase, K. *Bull. Chem. Soc. Japan* **1979,** *52*, 2737.
9 Yamakawa, K., Tomınaga, T ; Nıshitani, K *Tetrahedron Lett.* **1975,** 4137
10 Tamakawa, T., Nishıtani, K.; Tominaga, T *Tetrahedron Lett.* **1975,** 2829.
11. Ando, M.; Wada, T ; Kusaka, H.; Takase, K.; Hırata, N , Yanagi, Y. *J. Org Chem* **1987,** *52*, 4792
12. Honwad, V. K.; Siscovıc, E.; Rao, A. S *Tetrahedron* **1967,** *23*, 1273.
13 Ando, M , Tajıma, K.; Takase, K. *J. Org Chem.* **1983,** *48*, 1210.
14 Suchy, M.; Herout, H., Sorm, F. *Coll Csech. Chem. Commun.* **1964,** *29*, 1829.
15. Barton, D. H R.; Pınhey, J T.; Wells, R J. *J. Chem. Soc.* **1964,** 2518.
16. Ando, M.; Akahme, A.; Yamo, H., Takase, K. *J. Org Chem.* **1982,** *47*, 3909
17. White, E. H.; Eguchı, S., Marx, J. N. *Tetrahedron* **1969,** *25*, 2099
18 Marx, J. N.; Whıte, E. H. *Tetrahedron* **1972,** *28*, 2117
19 Marx, J. N.; McGaughey, S. M. *Tetrahedron* **1972,** *28*, 3583
20 Buchi, G.; Lowenthal, H. J. E. *Proc. Chem. Soc.* **1962,** 280.
21. Edgar, M. T., Greene, A. E.; Crabe, P *J. Org. Chem.* **1979,** *44*, 159.
22 Greene, A. E.; Muller, J. C., Ourisson, G. *J. Org. Chem* **1974,** *39*, 186.
23. Barton, D. H. R.; Moss, G P.; Whittle, J. A *J. Chem. Soc* **1968,** 1813.
24. Greene, A. E. *J. Am Chem. Soc.* **1980,** *102*, 5337.
25. White, E. H ; Eguchi, S ; Marx, J. N. *Tetrahedron* **1969,** *25*, 2099
26. Kabalka, G. W.; Yang, D T C.; Baker, Jr , J. D *J. Org. Chem* **1976,** *41*, 574.
27. Kabalka, G. W ; Baker, J. D ; Neal, G. W *J. Org Chem.* **1977,** *42*, 512
28 See Ref 27 (footnote).
29. Grıeco, P A ; Nogues, J. A , Masakı, U. *J Org. Chem.* **1977,** *20*, 495
30 Fujimoto, Y.; Miura, H., Shımızu, T.; Tatsuno, T *Tetrahedron Lett* **1980,** *21*, 3409.
31. Watabane, M.; Yoshikoshi, A *J. Chem. Soc Perkın Trans. I* **1987,** 1793.
32. Watanabe, M ; Yoshikoshı, A *J. Chem. Soc. Perkın Trans. I* **1987,** 2833.
33. Yamakawa, K.; Nishıtanı, K., Murakamı, A., Yamamoto, A. *Chem. Pharm Bull* **1983,** *31*, 3397.
34. Yamakawa, K.; Nishitanı, K , Murakamı, A., Yamamoto, A. *Chem. Pharm Bull.* **1983,** *31*, 3411.
35. Bruderer, H , Arigonı, D., Jeger, O. *Helv. Chim Acta* **1956,** *39*, 858.
36. Nozoe, T ; Asao, T.; Ando, M.; Takase, K *Tetrahedron Lett.* **1967,** 2821
37 Ando, M.; Asao, T ; Takase, K. *Tetrahedron Lett.* **1969,** 4689.
38 Ando, M ; Nanaumı, K , Nakagawa, T ; Asao, T ; Takase, K. *Tetrahedron Lett* **1970,** 3891
39 Pıers, E., Cheng, K F *Canad. J Chem* **1968,** *46*, 377
40. Howe, R , McQuillın, F. J. *J. Chem Soc* **1955,** 2423
41 Nakasakı, M. *Chem & Ind.* **1962,** 413.
42. Kate, K.; Nırata, Y.; Yamamura, S. *Tetrahedron* **1971,** *27*, 5987.
43 Sutherland, M D. *Aust J. Chem.* **1964,** *17*, 75.
44. Jones, R. V. H ; Sutherland, M. D. *Aust J. Chem.* **1968,** *21*, 2255.
45 Murai, A.; Nıshızakura, K.; Katsui, N ; Masamune, T. *Bull. Chem. Soc Japan* **1977,** *50*, 1206
46. Mıyashıta, M , Suzukı, T ; Yoshikoshi, A. *Chem. Lett.* **1987,** 2387
47. Mıyashita, M.; Suzukı, T ; Yoshıkoshı, A. *Tetrahedron Lett.* **1987,** *28*, 4293.
48 Harapanhallı, R. S. *J Chem Soc. Perkın Trans. I* **1988,** 2633.
49 Bertı, G In *Topics in Stereochemistry* Allinger, N L. and Elıel, E. L. (Eds), Wiley, New York, 1973, Vol 7, p 93.
50 Mıtsunobu, O., Eguchı, M *Bull Chem Soc. Japan* **1971,** *44*, 3427
51 Mıtsunobu, O *Synthesis* **1981,** 1
52 Cardona, L , Garcıa, B , Gıménez, E , Pedro, J R *Tetrahedron* **1991,** *48*, 851
53 Nıwa, M., Iguchı, M ; Yamamura, S. *Bull. Chem Soc Japan* **1972,** *49*, 3145