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SYNTHESIS OF CYCLOPENTA[*C*]PYRAN SKELETON OF IRIDOID LACTONES

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1. INTRODUCTION

The iridoids are large class of naturally occurring compounds with over 300 members in the family.[1] They represent a highly oxygenated monoterpenoid skeleton characterised by a functionalised cyclopentane ring *cis*-fused to a dihydropyran, δ-lactol or δ-lactone. The early examples of these cyclopentanoid monoterpenes, iridomyrmecin **1** and isoiridomyrmecin **2**,[2,3] were isolated almost five decades ago and have attracted considerable attention because of their diverse biological action and interesting structure. The name 'iridoid' originated from the fact that the first members were isolated from the secretion of ants belonging to the genus *Iridomyrmex*. An important place among the iridoids is held by loganin **5**, which is the biosynthetic precursor to secologanin **6**.[4] The monoterpene glycoside secologanin is the most important compound in alkaloid biosysnthesis which is not of amino acid origin. More than a thousand alkaloids are formed *in vivo* from secologanin. Secologanin is also the biogenetic key intermediate for the biosynthesis of secoiridoids, such as sweroside **7** and gentiopicroside **8**. The carbon skeleton of most iridoids and secoiridoids consists of nine or ten carbons; however, iridoid natural products with an unusual number of carbons, such as 8, 13, 14 or 19 are also known. Apart from the iridomyrmecins **1** and **2**, dihydronepetalactone **3** and isodihydronepetalactone **4** represent another type of cyclopentapyranones isolated from the volatile oils of the cat-attracting plant *Actinidia polygama*.[5] The stereochemistry at the four contiguous, asymmetric centres in iridomyrmecin and dihydronepetalactone and their congeners has attracted the attention of synthetic chemists for over three decades now.[1d] The first synthesis of iridoid lactones was published independently from the laboratories of Korte[6] and Robinson[7] in *Tetrahedron* in 1959. The synthesis of this physiologically active and structurally appealing class of iridoid monoterpenes continues to be an active area of research even today. They are small enough to be easily constructed and yet sufficiently complex structurally that their enantio- and stereoselective synthesis poses a challenge to a large and diverse set of chemists. These lactones lend themselves as suitable targets for the demonstration and application of new synthetic methodologies and protocols of the diastereoselective, asymmetric, organometallic and biogenetic variety. The focus in this review is to record the advances made in synthetic strategies to install the cyclopentapyranone skeleton of iridoid lactones. The classification, isolation, biological activity and biosynthesis of iridoid monoterpenes are briefly discussed in the early part of this report.

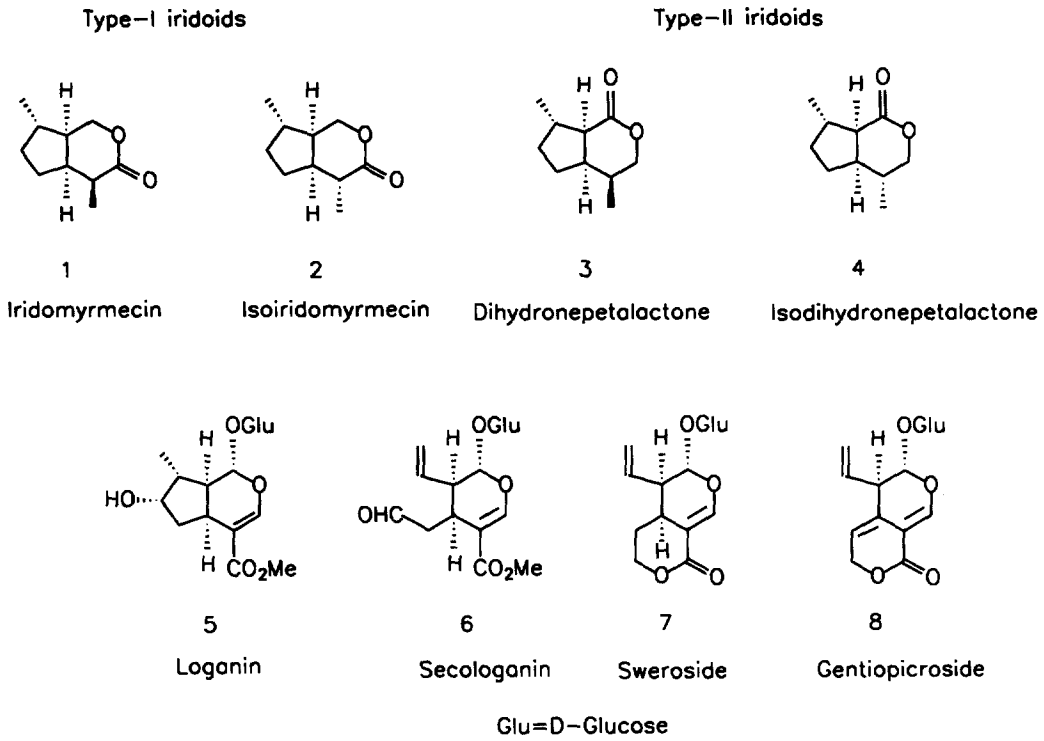


***Figure 1:** Some important iridoid lactones and biogenetic precursors*

2. CLASSIFICATION

The *cis*-linked partially hydrogenated cyclopenta[*c*]pyran skeleton characteristic to the iridoids has been drawn and numbered by earlier groups in different ways. Following (**9-12**) are some of the formulae and numbering systems employed in the literature.[4] Formula **11** is consistent with the biosynthetic evolution of iridoids as also their subsequent biotransformation to alkaloids, and hence it is the preferred representation and also used in this text. The current *Chemical Abstracts* nomenclature for heterocycle **11** is (1*R*,4a*S*,7*S*,7a*R*)-1-hydroxy-7-methyl-1,4a,5,6,7,7a-hexahydrocyclopenta[*c*]pyran-4-carboxylic acid, or simply "iridene".

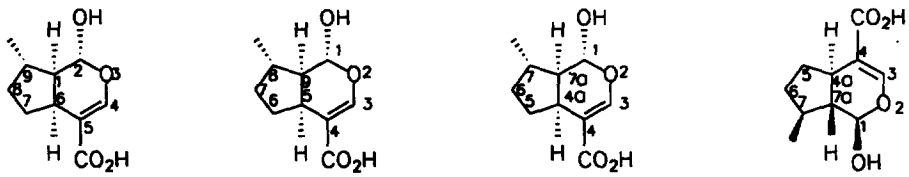


***Figure 2:** Numbering systems of iridoids*

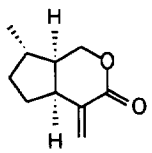
For the saturated *cis*-2-oxabicyclo[4.3.0]nonane skeleton, the name "iridane" is usually adopted. Most of the glycoiridoids, such as loganin **5**, are linked to D-glucose at C1 *via* a β-glycosidic bond.

In most of the known cyclopentapyranone natural products, the lactone is *cis*-fused to the functionalised cyclopentane ring. The absolute configuration at the three contiguous non-epimerisable stereogenic centres C4a, C7a and C7 is usually as shown for iridene **11**, although the actual designations, *R* or *S*, may vary depending on the nature of substitution or unsaturation on the bicyclic skeleton. The iridoid lactones can be further sub-divided into two groups, type-I and type-II,[8] depending on the regiochemical orientation of the lactone with respect to the functionalised cyclopentane ring. In type-I iridoids typified by iridomyrmecin **1** and isoiridomyrmecin **2** the lactone carbonyl is at C3, whereas in type-II lactones such as dihydronepetalactone **3** and isodihydronepetalactone **4** the carbonyl group is at C1.

3. NATURAL OCCURRENCE AND BIOLOGICAL ACTIVITY

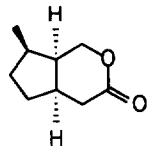
3.1 Type-I lactones

The ant lactones iridomyrmecin **1** and isoiridomyrmecin **2** were isolated from *Iridomyrmex humilis* Mayr and *Iridomyrmex nitidus* Mayr.[2,3] The epimeric lactones are used by ants as agents of defence against preying insects and as possible means of communication. They are found as minor components in the volatile oil of fresh fruits of the cat- and lacewing-attracting plant *Actinidia polygama* Miq.[5] In addition to these intriguing properties iridomyrmecin is known to be a potent insecticide and exhibits antibiotic action. Allodolicholactone **13** was isolated by Pagnoni and coworkers[9] from a wild plant *Teucrium marum* (Labiatae) that grows in the Mediterranean region and is characterised by a powerful lachrimatory essential oil. Lactone **13** was referred to as allodolicholactone in the earlier literature[9,10] and subsequently renamed as teucriumlactone.[11] Sakan *et al.*[12] isolated boschnialactone **14** as one of the physiologically active principles from *Boschniakia rossica* Hult. This lactone, too, has a marked physiological action on cats, similar to the constituents of *A. polygama*. Some of the recent and less common examples of type-I iridoids are isoepiiridomyrmecin **15**, dehydroiridomyrmecin **16** and isodehydroiridomyrmecin **17**.[13] In this diverse collection of diastereomeric type-I iridoids, a natural product corresponding to epiiridomyrmecin **18** has so far not been isolated.



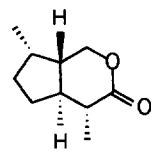
13

Teucriumlactone



14

Boschnialactone



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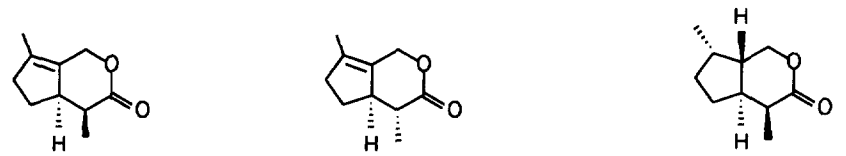
Isoepiiridomyrmecin



16 Dehydroiridomyrmecin

17 Isodehydroiridomyrmecin

18 Epiiridomyrmecin

Figure 3: Structures of type-I iridoid lactones

McConnel *et al.*[14] reported that the difference in the biological activity of isoiridomyrmecin, which has considerable cat-nip activity, and iridomyrmecin is not due to their epimeric relationship but is closely related to the overall shape of the molecules. The lactone ring is in a boat-like conformation in both the molecules; the tethered cyclopentanoid ring is *exo* in isoiridomyrmecin and *endo* in iridomyrmecin. As a result, isoiridomyrmecin is a relatively flat molecule with enhanced cat-nip activity compared to iridomyrmecin, which is markedly buckled.

Isoiridomyrmecin Iridomyrmecin

Figure 4: X-ray structure of iridomyrmecin and isoiridomyrmecin

3.2 Type-II lactones

Bates *et al.*[15] isolated nepetalactone **19** as the major component and its C7a-epimer **20** as the minor compound from the oil of cat-nip. The nepatalactones were degraded to nepetalic acids and nepetic acids. The enol lactone **21** was obtained as the major (95%) steam-volatile oil component from the foliage of *Nepeta mussini*.[16] The cat-attracting lactones dihydronepetalactone **3**, isodihydronepetalactone **4** and neonepetalactone **22**, along with iridomyrmecins **1** and **2**, were extracted from the leaves and galls of *Actinidia polygama*.[5] Further investigation with the same plant species yielded cat-nip compounds dihydroepinepetalactone **23**, isodihydroepinepetalactone **24** and isoneonepetalactone **25**.[13] The C6-hydroxylated lactone, boonein **26** was isolated from the bark of *Alstonia boonei*, a Nigerian tree of medicinal value.[17] The presence of boonein and indole alkaloids in the same plant is of great biogenetic interest. The cyclopentanoids mitsugashiwalactone **27** and onikulactone **28**[18] have a nine carbon skeleton and are isolated as the biologically active constituents of *Boschniakia rossica* and *Menyanthes trifoliata*. They are known to be highly attractive to the Felidae and Chrysopidae.

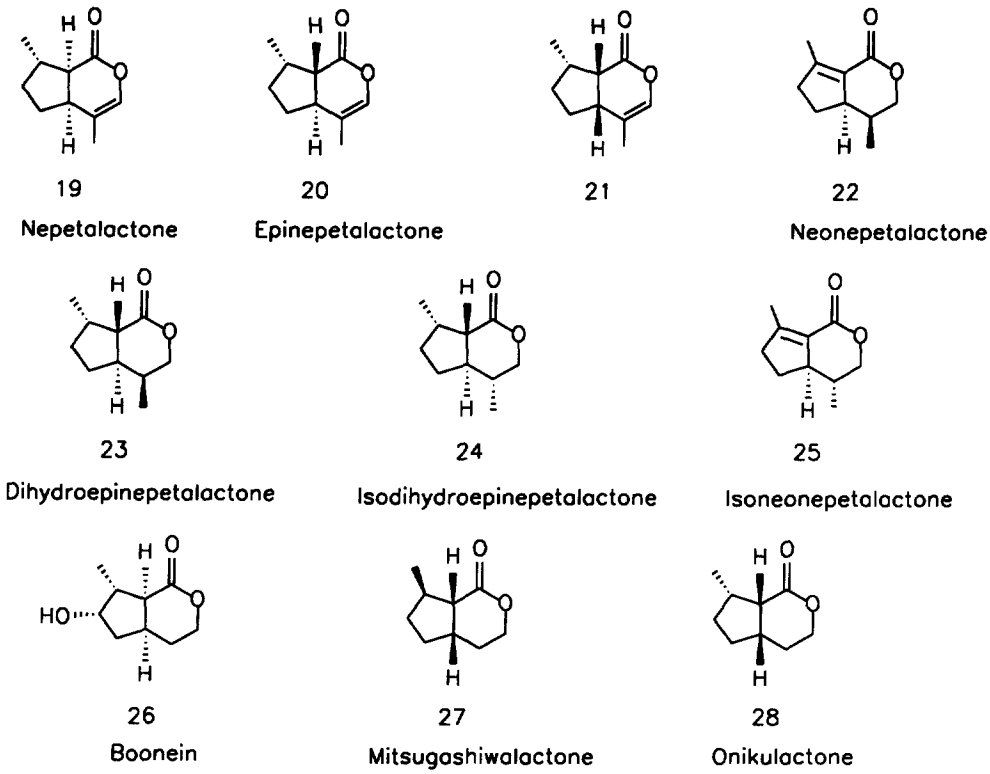
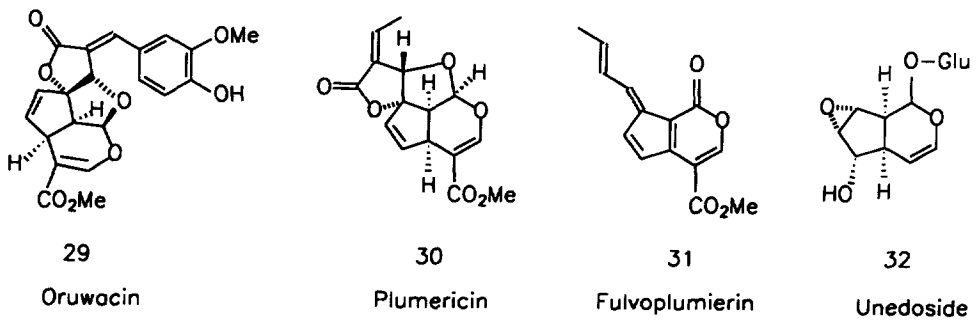
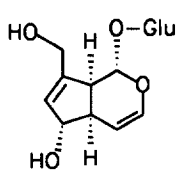


Figure 5: *Structures of type-II iridoid lactones*

3.3 Terpenoids and higher iridoids

The configuration at C7 is usually *S* in most metabolites; the *R* configuration is rare, *e.g.*, in boschnialactone **14** and mitsugashiwalactone **27**. The ring junction at C4a-C7a is usually *cis* except in the *epi* series of lactones wherein it is *trans*, such as in lactones **15**, **23** and **24**. Although most natural iridoids have the terpenoid ten carbon core boschnialactone **14**, mitsugashiwalactone **27** and onikulatone **28** are notable exceptions.





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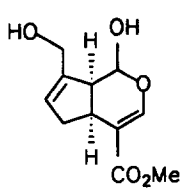
Aucubin



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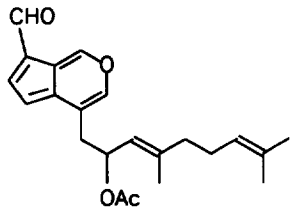
Genipin



35

Halitunal

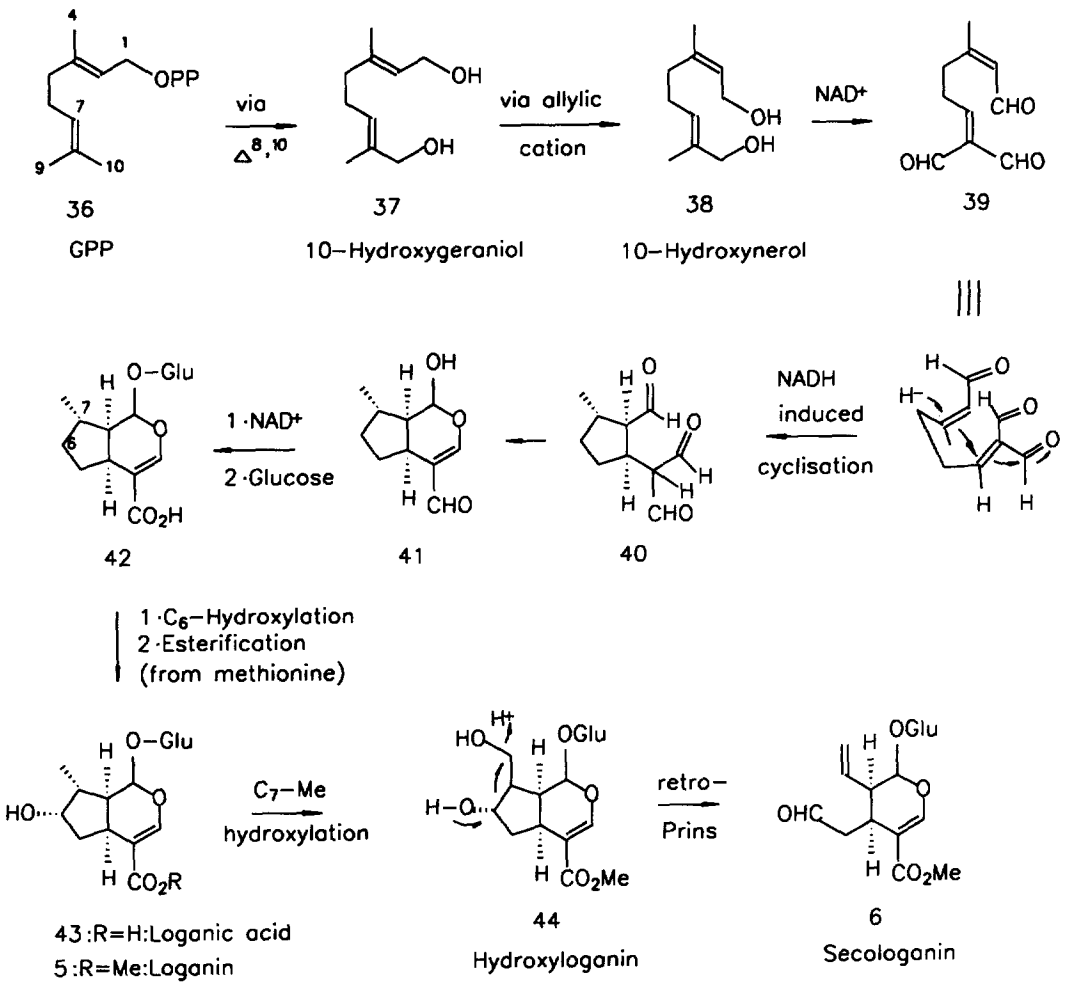
Figure 6: Structures of a few higher iridoids

Natural products in the iridoid family have been isolated with more exotic skeletons[4,19] such as oruwacin **29**, plumericin **30**, fulvoplumierin **31**, unedoside **32**, aucubin **33**, genepin **34** and halitunal **35**.

4. BIOSYNTHESIS

The biosynthesis of iridoids[20] has attracted the attention of many research teams for two main reasons: (i) good results can be obtained on incorporating labelled mevalonic acid precursors, and (ii) the close biogenetic relationship between the 10 (or 9) carbon core of iridoids and the skeletons of many indole and isoquinoline alkaloids. Loganin occupies a prominent position in iridoid biosynthesis because it is the precursor to secologanin and hence secoiridoids, *e.g.*, iridodial. The skeleton of secoiridoids is formally derived from iridoids by breaking the C6-C7 bond.

Biosynthetic studies carried out to date suggest that the most probable biosynthetic sequence from geraniol to loganin and secologanin is as follows:[20,21] Geranyl pyrophosphate **36** (GPP) is oxidised to 10-hydroxygeraniol **37** and then isomerised to 10-hydroxynerol **38**. The trialdehyde **39** derived from nerol undergoes a double Michael addition to yield the iridodial precursor **40** which undergoes cyclisation to lactol **41**; oxidation of the aldehyde and glycolysis of the lactol furnishes 6-deoxyloganinic acid **42**. It is not clear whether the two terminal carbons C9 and C10 of geraniol are both aldehydes or an aldehyde and an acid in **39**. It is also possible that the double Michael addition takes place on the isomeric *trans*-trialdehyde derived from geraniol directly. However, the observation that 10-hydroxynerol **38** is a more efficient precursor than 10-hydroxygeraniol **37** argues in favour of nerol as an intermediate. Oxidation of **42** at C6 to loganinic acid **43** can be rationalised on the basis of a conformationally favourable 1,5-hydride shift. The next oxidation of the 'unactivated methyl' group of loganin **5** to hydroxy loganin **44** is more tricky and perhaps takes place *via* oxidation, hydration and reduction sequence. Cleavage of the C6-C7 bond of loganin **5** to produce secologanin **6** is visualised as a retro-Prins reaction on intermediate **44**. The water-soluble glucosides loganin and secologanin are the biogenetic precursors to iridoids and secoiridoids, respectively.

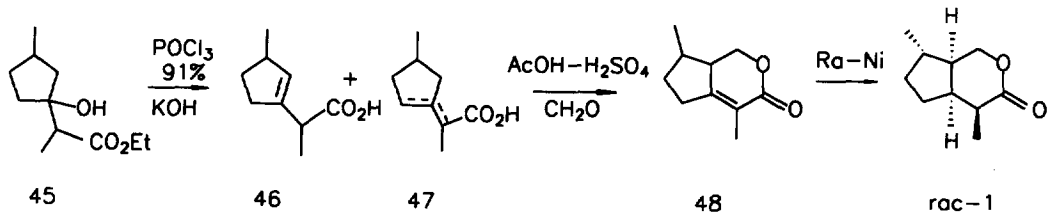


Scheme 1: Biosynthesis of loganin and secologanin from geraniol

5. SYNTHESIS OF TYPE-I IRIDOID LACTONES

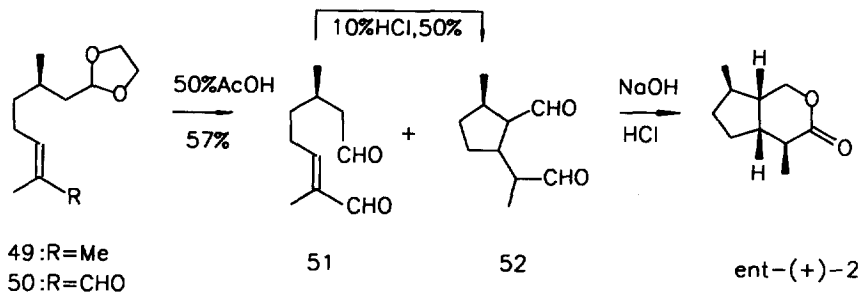
5.1 The early approaches

Reformatsky reaction of 3-methylcyclopentanone with ethyl α-bromopropionate afforded the hydroxy ester **45** (84%) which was dehydrated with $POCl_3$ to an alkenic ester and hydrolysed to the corresponding acid **46**. Prins reaction of the β,γ-unsaturated acid **46** in presence of formaldehyde afforded the unsaturated lactone **48**, which upon Raney-Nickel reduction afforded *rac*-iridomyrmecin **1**.[6] The synthesis was complicated by the fact that a mixture of olefin regioisomers (such as **47**) were produced at each stage and the final product was isolated in pure form after careful crystallisation from petroleum ether.



Scheme 2: Korte synthesis of (±)-1

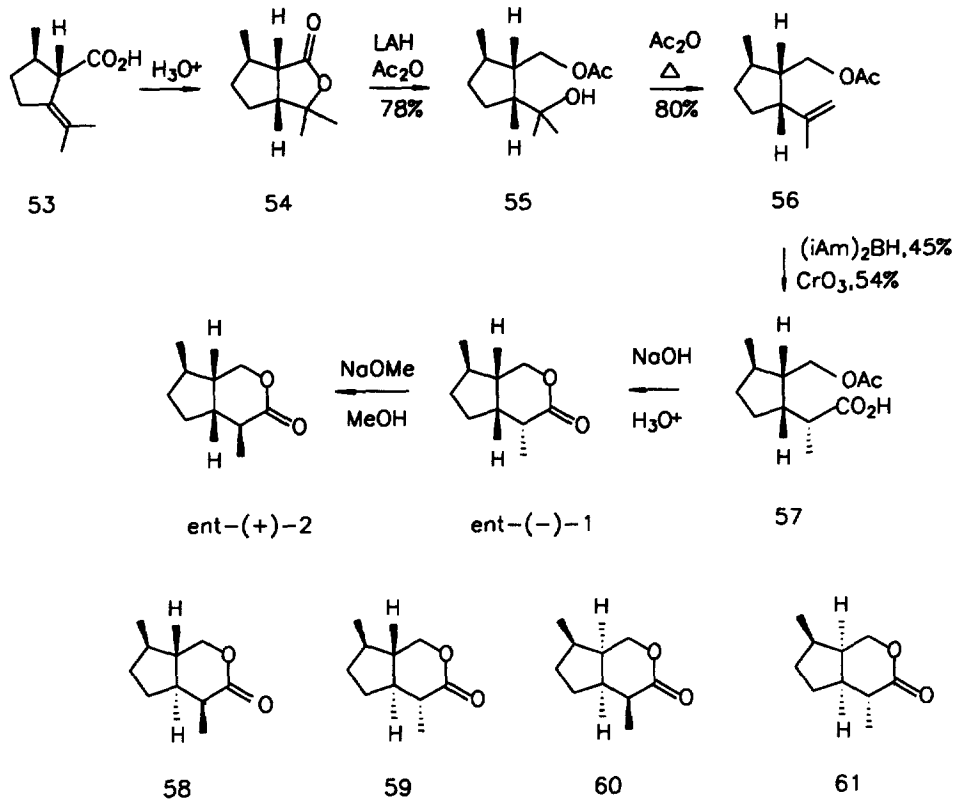
The ethylene acetal **49** of D-citronellal was oxidised with SeO_2 to the α,β-unsaturated aldehyde **50** (40%) which was deprotected with aqueous AcOH to produce a 1:1 mixture of isomeric dialdehydes **51** and **52**. Dialdehyde **51** could be cyclised with dilute HCl to produce iridodial **52** in ~50% yield. Treatment of iridodial **52** with hot alkali afforded the two possible Cannizaro products; the isomeric hydroxy acids cyclised to a mixture of bicyclic δ-lactones from which *ent*-(+)-isoiridomyrmecin **2** was isolated by recrystallisation.[7]



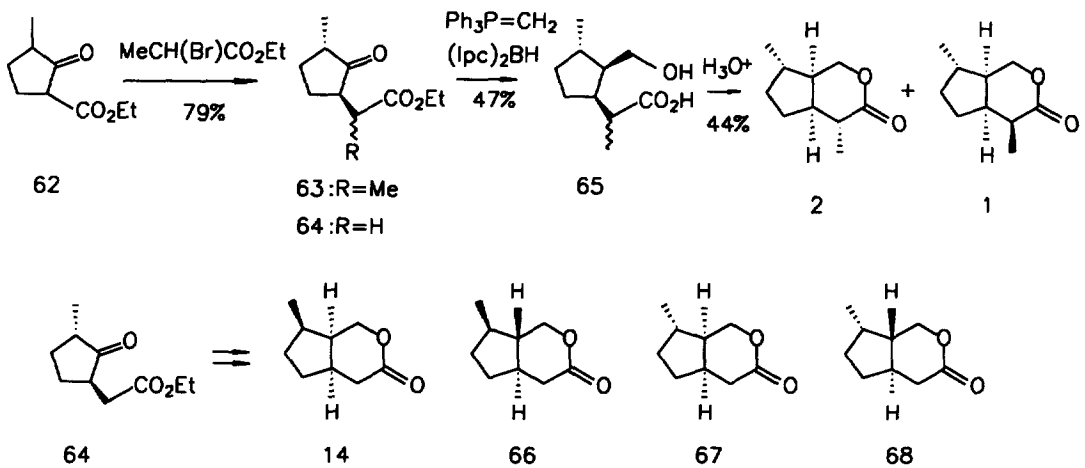
Scheme 3: Robinson synthesis of ent-(+)-2

Wolinsky *et al.*[22] synthesised six of the eight possible stereoisomers of iridolactones starting from *anti*-pulegenic acid **53**, prepared *via* a Favorskii rearrangement on the dibromide of *(R)*-pulegone. Heating *anti*-pulegenic acid **53** with dilute HCl cleanly afforded *cis-anti*-pulegenolide **54** which contains the correct arrangement of the three asymmetric centres on the cyclopentane ring. LAH reduction of lactone **54** to the diol and conversion to monoacetate **55** was uneventful. Dehydration of the tertiary alcohol under hot acetylation conditions afforded a 4:1 mixture of the desired isopropenyl cyclopentane **56** and the isopropylidene isomer in 80% yield. Highly stereoselective hydroboration-oxidation to acid **57** and lactonisation furnished *ent*-(-)-iridomyrmecin **1**. Epimeristaion of iridomyrmecin with base afforded the more stable *ent*-(+)-isoiridomyrmecin **2**. Stereoisomers of the natural iridolactones, such as *trans-anti*-lactones **58**,**59** and *cis-syn*-lactones **60**,**61** were also synthesised using related methodology.

2-Carbethoxy-5-methylcyclopentanone **62** was elaborated to a stereorandom propionate mixture of *anti*-2,5-disubstituted cyclopentanones **63**. Wittig methylenation of the ketone and hydroboration-oxidation afforded *cis-anti*-2-(2-hydroxymethyl-3-methylcyclopentyl)propionic acid **65** in 47% yield. Cyclisation of δ-hydroxy acid **65** afforded a mixture of epimeric *rac*-iridomyrmecins **1** and **2**.[23a]



Scheme 4: Wolinsky synthesis of ent-(-)-1 and ent-(+)-2

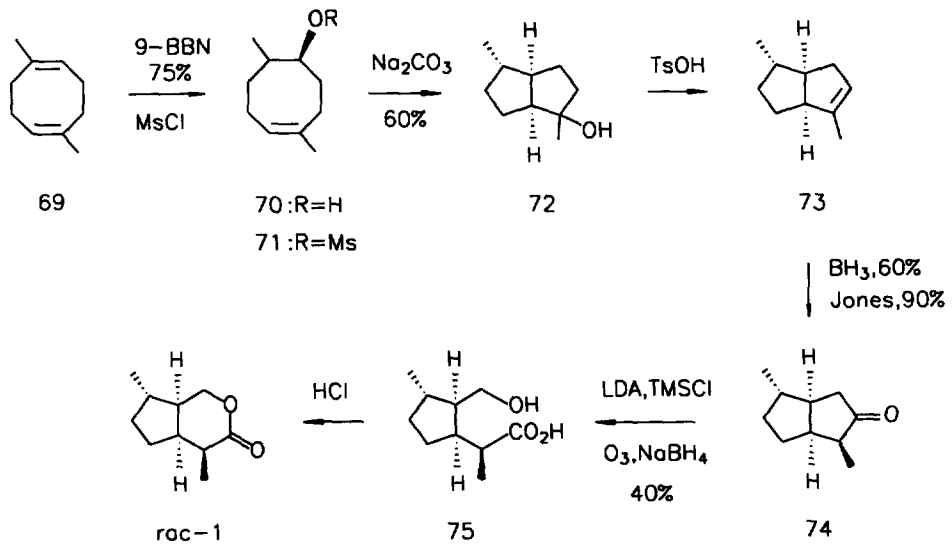


Scheme 5: Sisido synthesis of (±)-1, (±)-2 and (±)-14

Bicyclic lactones with a *trans* ring junction were synthesised by condensation of ketone **63** with $Ph_3P{=}CH(OMe)$ followed by hydrolysis, borohydride reduction and lactonisation. A few years later the same research group reported[23b] the synthesis of boschnialctone **14** and its stereoisomers **66**, **67** and **68** starting from ethyl (2-oxo-3-methylcyclopentyl)acetate **64** based on a similar protocol.

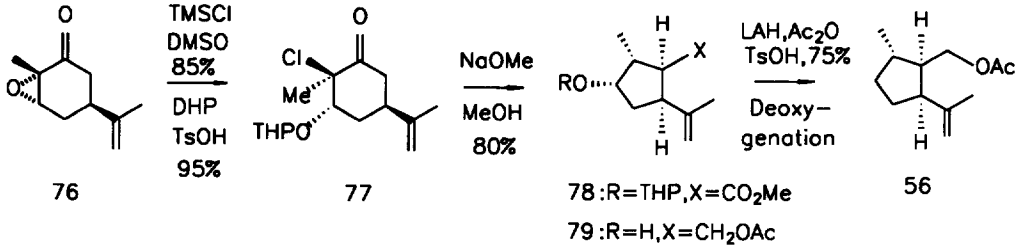
5.2 Ring contractions

Selective monohydroboration-oxidation of 1,5-dimethyl-1,5-cyclooctadiene **69** with 9-BBN to alcohol **70** took place in 75% yield. The mesylate **71** was solvolysed to the desired *exo*-methyl and *cis*-fused bicyclo[3.3.0.]octane system **72**.[24] The stereochemical control in the cyclisation is attributed to the π-electron participation in the solvolytic removal of the leaving group (OMs) and thus the *exo* orientation of the methyl group is a consequence of its *anti* relationship to the mesylate. Alcohol **72** was regioselectively dehydrated to olefin **73** and subjected to hydroboration-oxidation sequence to cyclopentanone **74**. Ozonolysis of the kinetic silylenol ether, reduction to hydroxy acid **75** and lactonisation yielded *rac*-iridomyrmecin **1** whose C4-epimerisation provided *rac*-isoiridomyrmecin **2**.



Scheme 6: Whitesell synthesis of (±)-1 and (±)-2

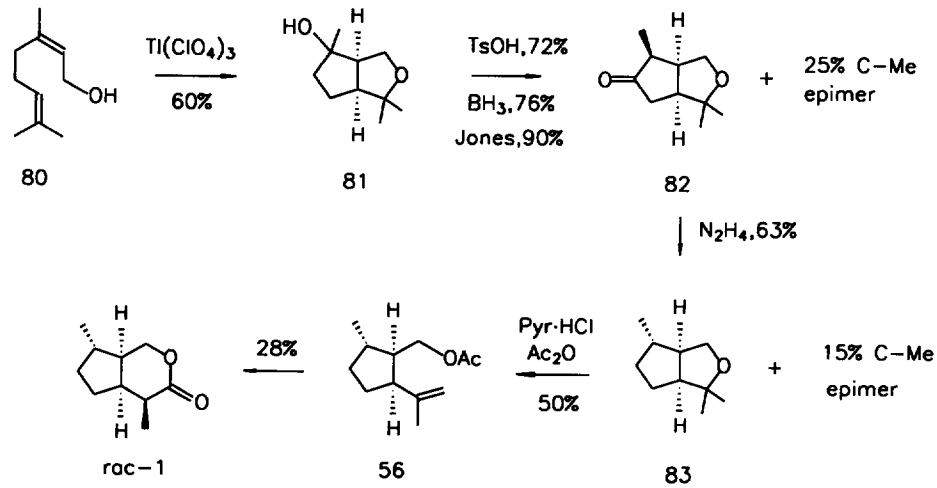
The monoepoxide **76** of (+)-carvone was treated with TMSCl and the resulting chlorohydrin converted to the THP ether **77**. Favorskii ring contraction of **77** with NaOMe afforded the requisite cyclopentanecarboxylate **78** with high stereoselectivity (>10:1).[25] The contiguous methyl, carbomethoxy and isopropenyl groups on cyclopentane **78** are correctly oriented for natural iridolactones. Sequential treatment of **78** to reduction, acetylation and deprotection conditions afforded hydroxy acetate **79**, which was deoxygenated to **56**, a known intermediate[22] in the synthesis of (+)-iridomyrmecin **1**.



Scheme 7: Lee synthesis of (+)-1

5.3 Biogenetic type

Geraniol **80** was cyclised using thallium(III) perchlorate to an isomeric mixture of oxabicyclo[3.3.0]octanes **81** (49% and 11%), in which the undesired *endo*-methyl epimer predominated.[26] Deoxygenation of tertiary alcohol **81** was carried out by a rather circuitous route to favour formation of the desired and more stable *exo*-methyl epimer **83**. Cleavage of the tetrahydrofuran ring by treatment with pyridine hydrochloride in refluxing acetic anhydride gave a 1:1 mixture of isopropenyl derivative **56** and its isopropylidene isomer in near quantitaive yield. The Wolinsky[22] intermediate **56** and was transformed to *rac*-iridomyrmecin **1** in 28% yield.

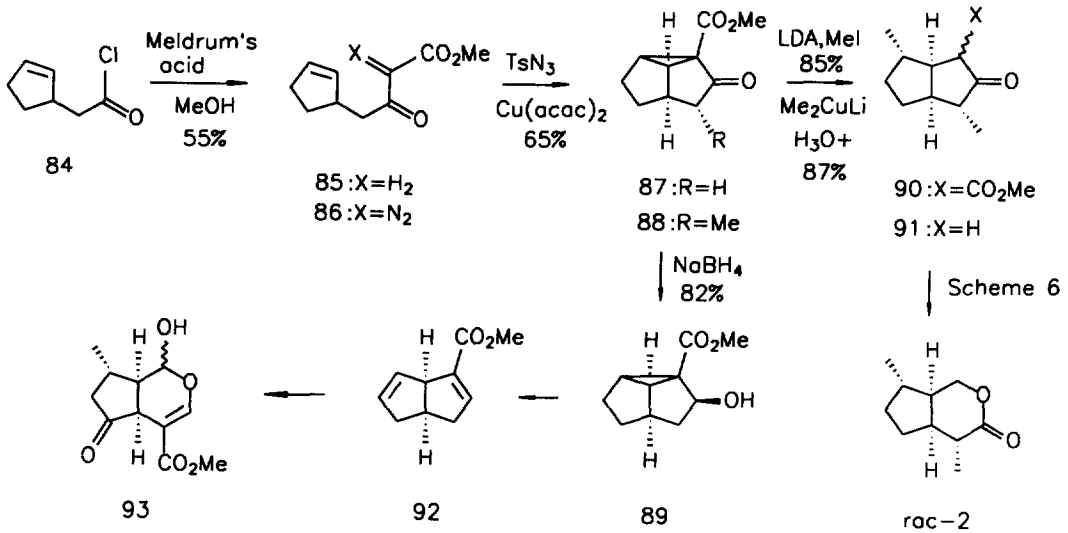


Scheme 8: Yamada synthesis of (±)-1

5.4 Cyclopropane ring cleavage

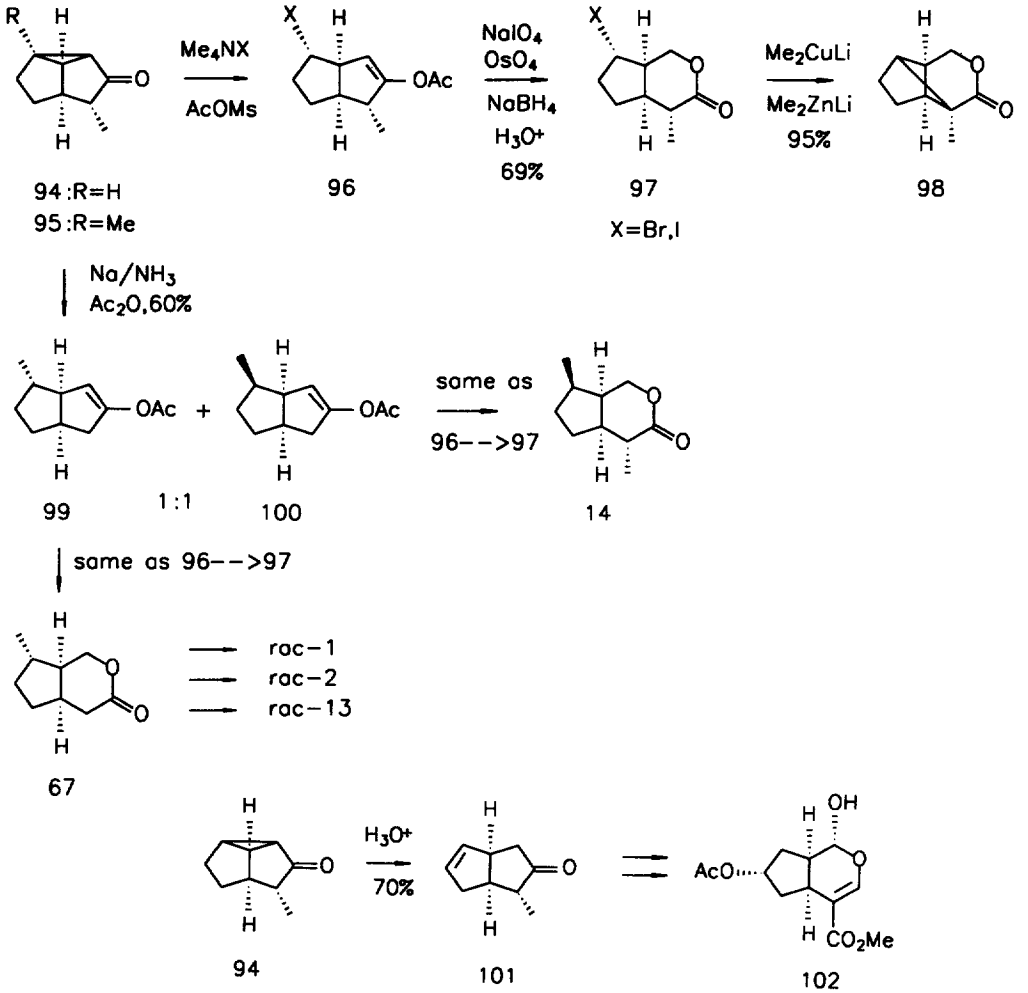
In the early 1980s, three synthetic routes were independently published[10,27,28] based on the same theme: the stereoselective opening of cyclopropane ring in tricyclo[3.3.0.$0^{2,8}$]octane derivatives to bicyclo[3.3.0]octanes. The difference lay in the way in which each group synthesised the crucial tricyclic synthon.

The acid chloride **84** of 2-cyclopentene-1-acetic acid was transformed to β-keto ester **85** and then converted to the diazo compound **86** with *p*-TsN_3. Cyclopropanation of the incipient carbene generated with $Cu(acac)_2$ afforded the desired tricyclic ketone **87**.[27] Sodium borohydride reduction of ketone **87** afforded the expected *endo*-alcohol **89** in 82% yield. In accord with this stereochemical preference, kinetic enolisation of ketone **87** (LDA) and MeI quench led exclusively to product **88**. Diastereoselective, conjugate cyclopropane ring opening with Me_2CuLi, hydrolysis and decarboxylation of keto ester **90** produced a single stereoisomeric ketone **91**. The Whitesell[24] sequence furnished *rac*-isoiridomyrmecin **2** from ketone **91**. In addition, hydroxy ester **89** was solvolysed to diquinane **92** for eventual conversion to *rac*-verbenalol **93**.



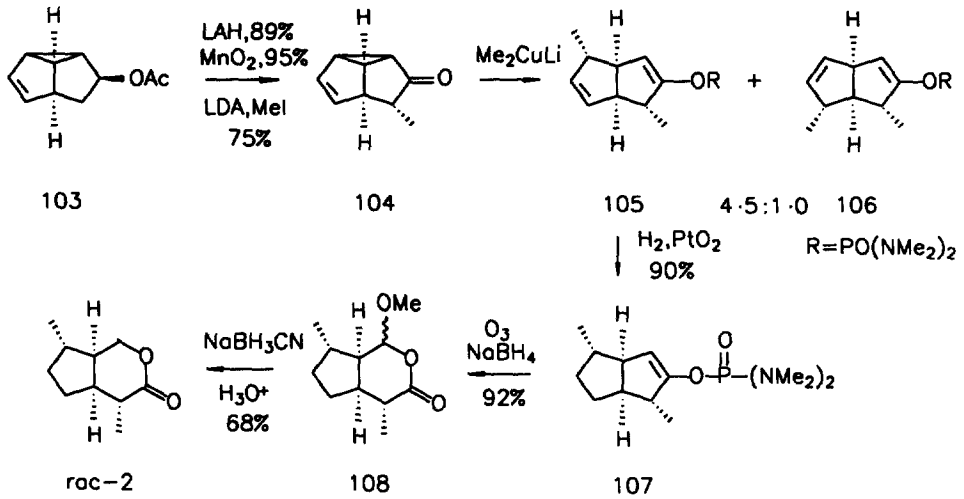
Scheme 9: Vandewalle synthesis of (±)-2

The cyclopropane ring in methylated ketone **94** was cleaved to the halo derivative **96** (X=Br,I). Enol acetate **96** was oxidised with $OsO_4/NaIO_4$ and reduced with $NaBH_4$ to halolactone **97**.[10] Attempts to exchange the halogen atom in **97** with methyl group proved unfeasible because the undesired tricyclic lactone **98** was formed readily by intramolecular displacement of lactone enolate on the C7-halogen. A modified route was successful in producing the iridoid lactones but lacked stereoselectivity. Thus, Birch reduction of tricyclic ketone **95** opened the cyclopropane ring regiospecifically but afforded a 1:1 mixture of diastereomers **99** and **100** at the C-Me centre. Both the stereoisomers were serviceable in that the *endo*-methyl compound **100** was elaborated to *rac*-boschnialactone **14** and the *exo*-methyl substrate **99** was transformed to cyclopentapyranone *rac*-**67**. The homologation of **67** to *rac*-teucriumlactone **13** and subsequently to *rac*-iridomyrmecin **1** and *rac*-isoiridomyrmecin **2** was straightforward. In addition, the chiral tricyclic ketone (-)-**94** was enantiospecifically transformed to (+)-**102**, the aglycone 6-acetate of loganin **5**.



Scheme 10:** Demuth synthesis of (±)-**1**, (±)-**2**, (±)-**13**, (±)-**14** and (±)-**67

Photolysis of benzene and vinyl acetate produced **103** in low yield after silica gel purification.[28] The tricyclic adduct **103** was deprotected with $LiAlH_4$, oxidised with MnO_2 and kinetically methylated to the product **104** with complete stereocontrol. Reaction of **104** with Me_2CuLi and subsequent trapping of the enolate produced a 4.5:1.0 mixture of the desired 1,5-*exo*-addition product **105**, and the isomeric 1,7-*exo*-addition adduct **106**. The ratio of **105** to **106** suggests that the sterically unfavourable sp^3-sp^3 interaction (1,7-mode) is more severe than the sp^3-sp^2 interaction (1,5-mode). Selective hydrogenation of the more reactive olefin of major adduct **105** proceeded uneventfully to enol phosphate **107**. Ozonolysis of **107** in MeOH and reductive work-up with $NaBH_4$ gave anomeric pseudoesters **108** which were reduced with $NaBH_3CN$ to *rac*-isoiridomyrmecin **2**.

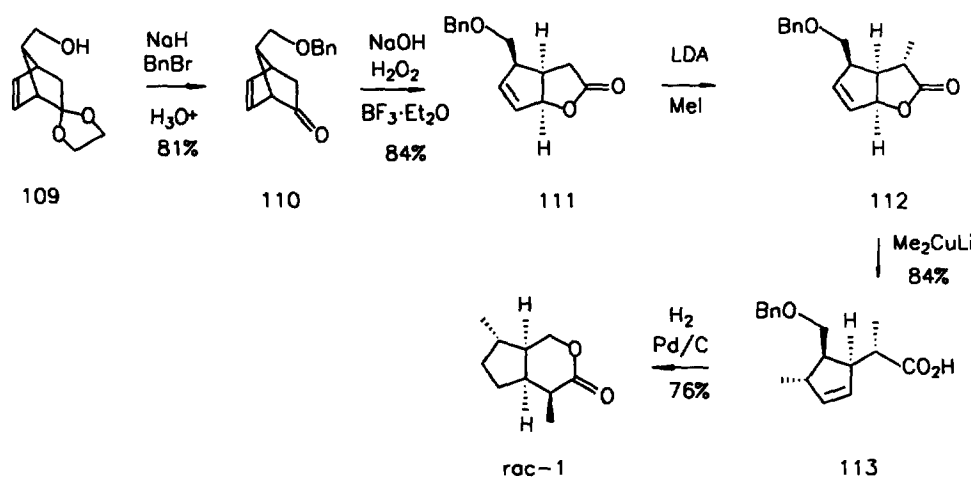


103 104 105 106 rac-2 108 107

Scheme 11: Wender synthesis of (±)-2

5.5 Norbornane template

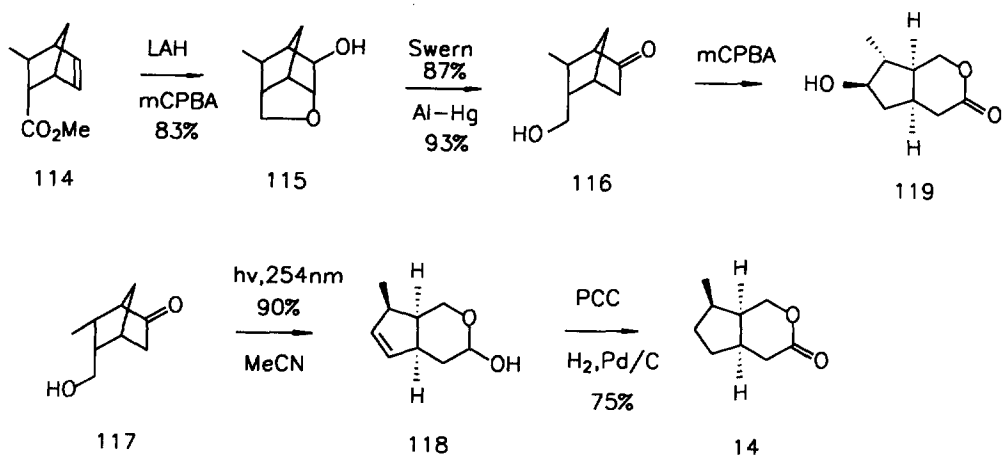
The bicyclo[2.2.1]heptane derivative **109** was converted to ketone **110** which upon treatment with basic H_2O_2 and exposure of the resultant hydroxy acid to $BF_3.Et_2O$ afforded the crystalline bicyclic lactone **111**.[29] Kinetic alkylation of lactone **111** afforded the anticipated *exo*-methyl compound **112**. Coupling of allylic lactone **112** with Me_2CuLi afforded a single carboxylic acid **113** which was exposed to hydrogenation conditions. Simultaneous reduction of the alkene, cleavage of the benzyl ether, and lactonisation of the hydroxy acid occurred to furnish a crystalline sample of *rac*-iridomyrmecin **1**. Thus, the four well defined, contiguous, stereogenic centres on the cyclopentapyranone skeleton unequivocally established the *anti*-S_N2' mode of coupling between cuprate and allylic lactone.



109 110 111 112 rac-1 113

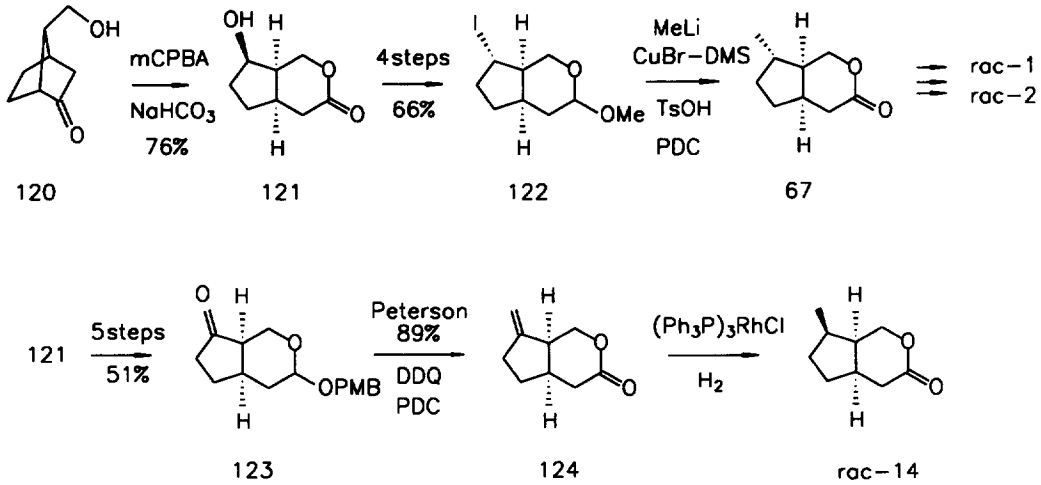
Scheme 12: Grieco synthesis of (±)-1

The *anti* norbornene ester **114** was reduced with LAH and cyclised with *m*-CPBA *via* the incipient epoxide to hydroxy norbornane **115**. Swern oxidation followed by reductive cleavage of the ether bond afforded the desired norbornanone **116**.[11] The epimeric *syn*-norbornanone **117** was obtained by a similar, though somewhat longer route, from the Diels-Alder adduct of cyclopentadiene and maleic anhydride. The photochemical Norrish I type reaction[30] of **117** in CH_3CN furnished lactol **118** in >90% yield. Routine PCC oxidation of the lactol and alkene hydrogenation gave *rac*-boschnialactone **14** in 75% overall yield. Isomer **116** was analogously transformed to cyclopentapyranone **67**, the penultimate precursor to iridomyrmecin **1**, isoiridomyrmecin **2** and teucriumlactone **13**.[10] Baeyer-Villiger oxidation of **116** and spontaneous translactonisation produced 6-hydroxy cyclopentapyranone **119**, an intermediate of interest in iridoid lactones.



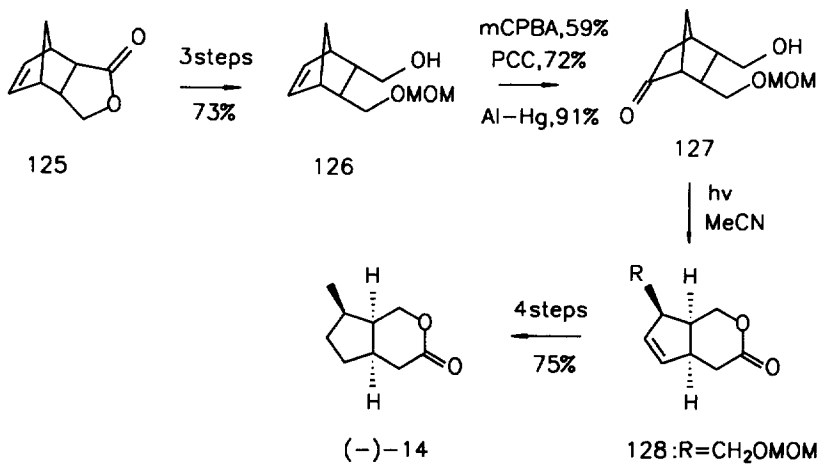
Scheme 13: Vandewalle synthesis of (±)-14 and (±)-67

The rearrangement of bicyclo[2.2.1]heptanone derivative **120** with *m*-CPBA did not stop at the Baeyer-Villiger product but proceeded through transesterification to the desired cyclopentapyranone **121** in 76% yield.[31] Introduction of the C7 methyl group was somewhat troublesome and was completed by a circuitous route necessitating lactone protection to supress the alternate intramolecular displacement pathway (see **97→98** in Scheme 10). Elaboration of lactol **122** to cyclopentapyranone **67** followed by homologation to *rac*-iridomyrmecin **1** and *rac*-isoiridomyrmecin **2** was uneventful. Comparison of the target lactones with natural iridoids served to confirm the single electron transfer induced *syn* coupling of methyl cuprate with iodide **122**. In addition, hydroxy lactone **121** was converted to keto lactol **123**, methylenated at C7 and oxidised to lactone **124**. Wilkinson hydrogenation of the exocyclic alkene gave rise to *rac*-boschnialactone **14** in which the C7-methyl group is shielded in the *endo* fold of the bicyclic skeleton.



Scheme 14: Wang synthesis of (±)-1, (±)-2, and (±)-14

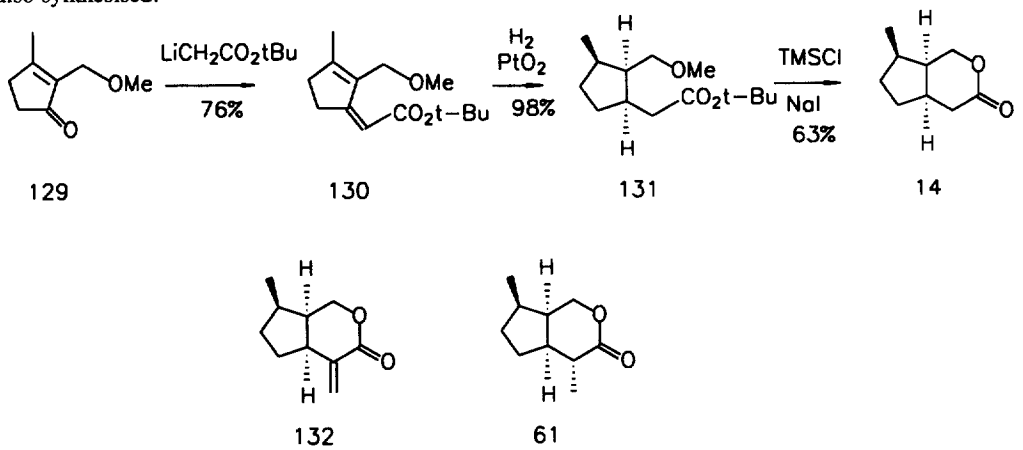
The chiral norbornene lactone **125** was synthesised by an asymmetric Diels-Alder reaction. Saponification of lactone **125**, diazomethane esterification, MOM etherification and LAH reduction afforded the monoprotected chiral diol **126**.[32] Exposure of alcohol **126** to *m*-CPBA gave the tricyclic ether which was oxidised (PCC) and the ether cleaved reductively (Al-Hg) to keto alcohol **127**. A Norrish I type cleavage[30] of ketone **127** resulted in the expected bicyclic lactol[11] which was oxidised to lactone **128**. The hydroxymethyl group was reduced to a methyl group *via* the tosylate and the alkene hydrogenated with 5% platinum on alumina to furnish (-)-boschnialactone **14**. The use of palladium or iridium catalyst caused significant epimerisation at C7-methyl centre or gave capricious yields.



Scheme 15: Koizumi synthesis of (-)-14

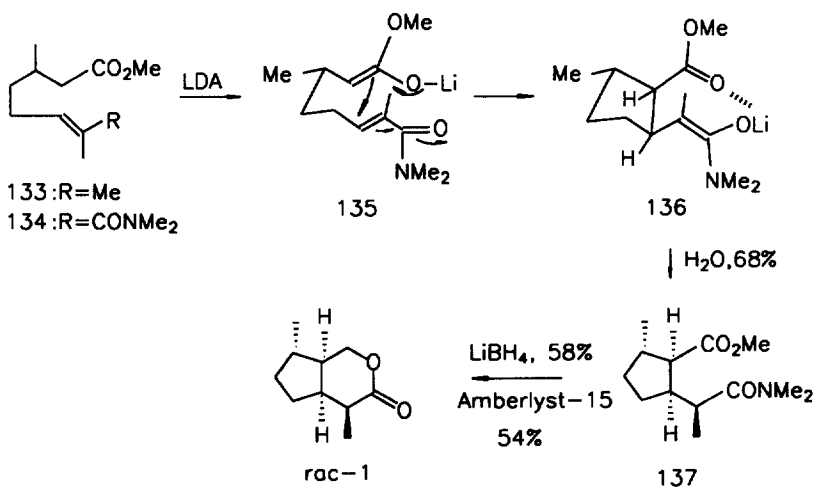
5.6 Stereoselective C-C and C-H bond formation

Low temperature condensation of 2-methoxymethyl-3-methyl-2-cyclopenten-1-one **129** with $LiCH_2CO_2Bu^t$ gave diene ester **130** and hydrogenation of the diene with Pt/C in EtOAc furnished **131** with the correct stereogenic centres at C7, C7a and C4a in a single step.[33] Methyl ether deprotection and cyclisation took place in the same step with TMSCl/NaI in refluxing MeCN to *rac*-boschnialactone **14**. The C4 homologs of boschnialactone, 7-epiteucriumlactone **132** and 7-epiisoiridomyrmecin **61**, were also synthesised.



Scheme 16: Guilard synthesis of (±)-14

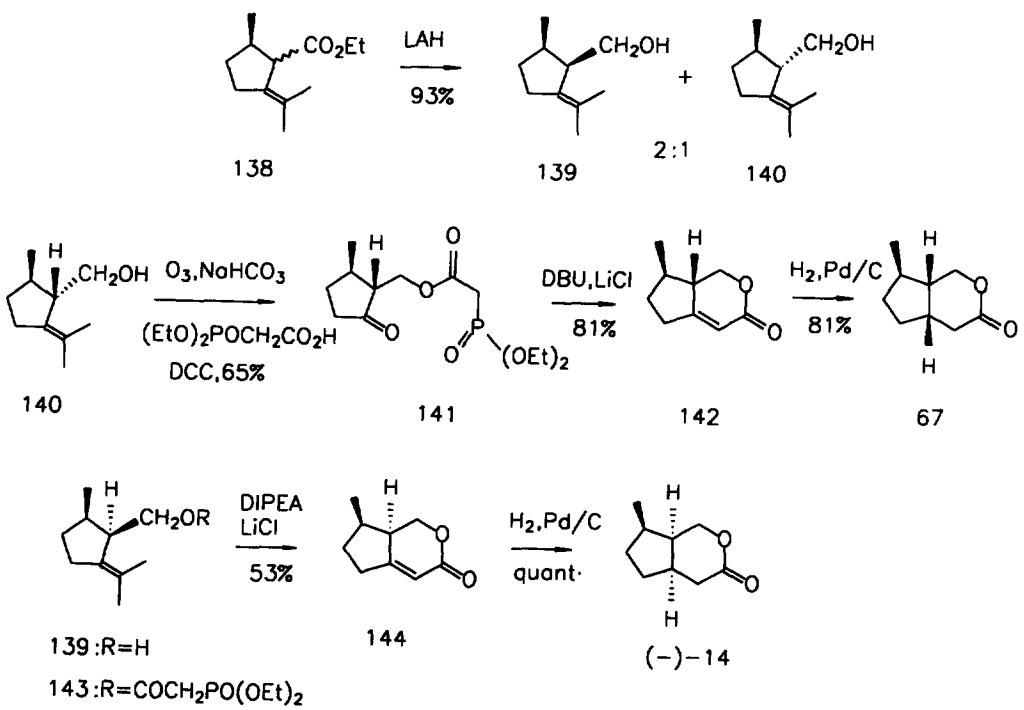
Methyl (±)-citronellate was converted to ester amide **134** which contains α,β-unsaturated amide as the Michael acceptor and ester group as the donor.[34]



Scheme 17: Yokoyama synthesis of (±)-1

The Michael donor-acceptor substrate **134** was treated with LDA to give a single diastereomeric adduct **137** *via* the favourable transition state **135** which experiences minimal $A^{(1,3)}$ strain[35] and maximal overlap of reacting orbitals. The newly formed amide enolate exists as the chelated conformation **136** fixed by the lithium cation. Aqueous quench of **136** produced ester **137** which was reduced to the alcohol and cyclised to give *rac*-iridomyrmecin **1**.

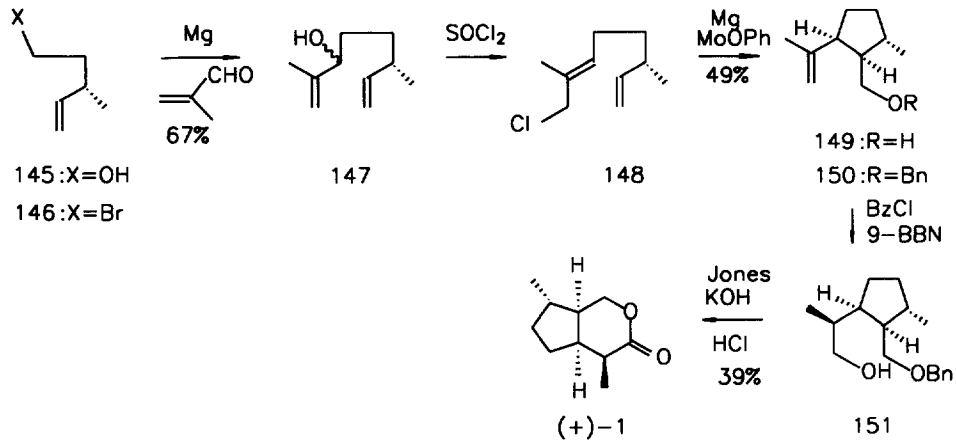
LAH reduction of the Wolinsky[22] ester **138** afforded *syn* (56%) and *anti* (37%) homoallylic alcohols **139** and **140**. The *anti*-alcohol **140** was independently prepared from pulegenate **53** in 82% yield. The *anti*-hydroxymethyl cyclopentane **140** was ozonised and esterified to phosphonate **141** under neutral conditions. Intramolecular Horner reaction of phosphonate in the presence of DBU and LiCl afforded the unsaturated δ-lactone **142** in 57% yield.[8,36] Highly stereoselective *exo* face hydrogenation installed the third stereogenic centre and furnished cyclopentapyranone (-)-**67**, the penultimate precursor to iridoids *ent*-(-)-**1**, *ent*-(+)-**2**, *ent*-(-)-**13**. A formal synthesis of the natural iridolactones was completed by synthesising (+)-**67** from *(S)*-pulegone, in turn prepared from *(S)*-citronellol. In an analogous manner, the *syn*-isomer **139** was transformed to natural (-)-boschnialactone **14**, the only modification being that the weaker DIPEA/LiCl conditions were used instead of DBU/LiCl. Exposure of phosphonates **141** and **143** to stronger, conventional bases such as NaH, *t*-BuOK, NaOEt, LiOH, Cs_2CO_3, LiHMDS, K_2CO_3, KOH, etc. in the Horner reaction resulted in extensive α-epimerisation and/or β-elimination.



Scheme 18: Nangia synthesis of (-)-14 and (-)-67

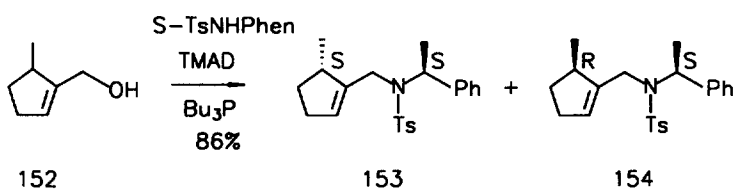
5.7 Sigmatropic rearrangements

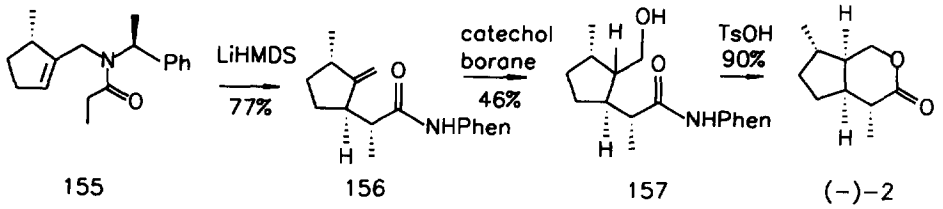
The potential of sigmatropic rearrangements in the stereocontrolled construction of naturally occurring carbon skeletons is well documented.[37] *(S)*-3-Methyl-1-penten-5-ol was converted to the corresponding bromide **146**, metalated to give the Grignard reagent and treated with methacrolein to furnish a 1:1 mixture of dienols **147**. The Mg-ene reaction on the rearranged chloride **148** and MoOPh trapping furnished alcohol **149** as the major component.[38] Benzoylation and hydroboration afforded monoprotected diol **151** which was oxidised to the acid, the benzoate group hydrolysed, and the hydroxy acid lactonised to give enantiomerically pure (+)-iridomyrmecin **1**. The diastereoselectivity in the Mg-ene process is rationalised by the favourable disposition of the secondary methyl group in pseudoequatorial position.



Scheme 19: Oppolzer synthesis of (+)-1

dl-2-Methyl-1-(hydroxymethyl)cyclopentene **152** was condensed with *N-(S)*-1-phenylethyltosylamide to afford a 1:1 mixture of *SS* and *RS* diastereomers **153** and **154** which were resolved by recrystallisation from hexane. The desired *(SS)*-**153** was converted to the aza-Claisen precursor **155** by Birch reduction of the tosylamide followed by acylation with propanoic anhydride (85%). Stereospecific amide enolate Claisen rearrangement of **155** afforded *(RR)*-**156** cleanly.[39] The excellent face selectivity in the sigmatropic rearrangement is a consequence of the cooperative double stereodifferentiation of the *(S)*-phenylethyl group on the auxiliary and the *(S)*-methyl group on the cyclopentene ring. Hydroboration of alkene **156** to hydroxy amide **157** and acid hydrolysis afforded (-)-isoiridomyrmecin **2**.

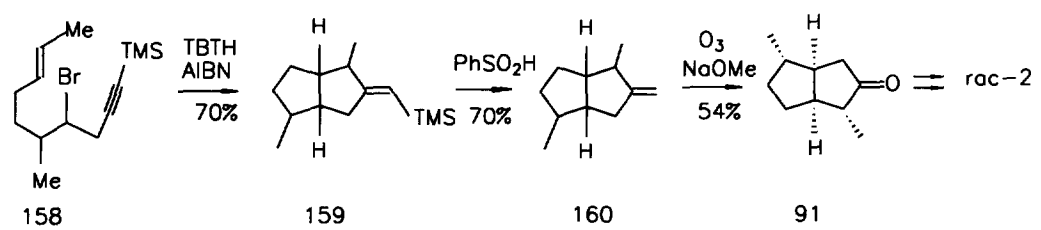




Scheme 20: Tsunoda synthesis of (-)-2

5.8 Radical cyclisations

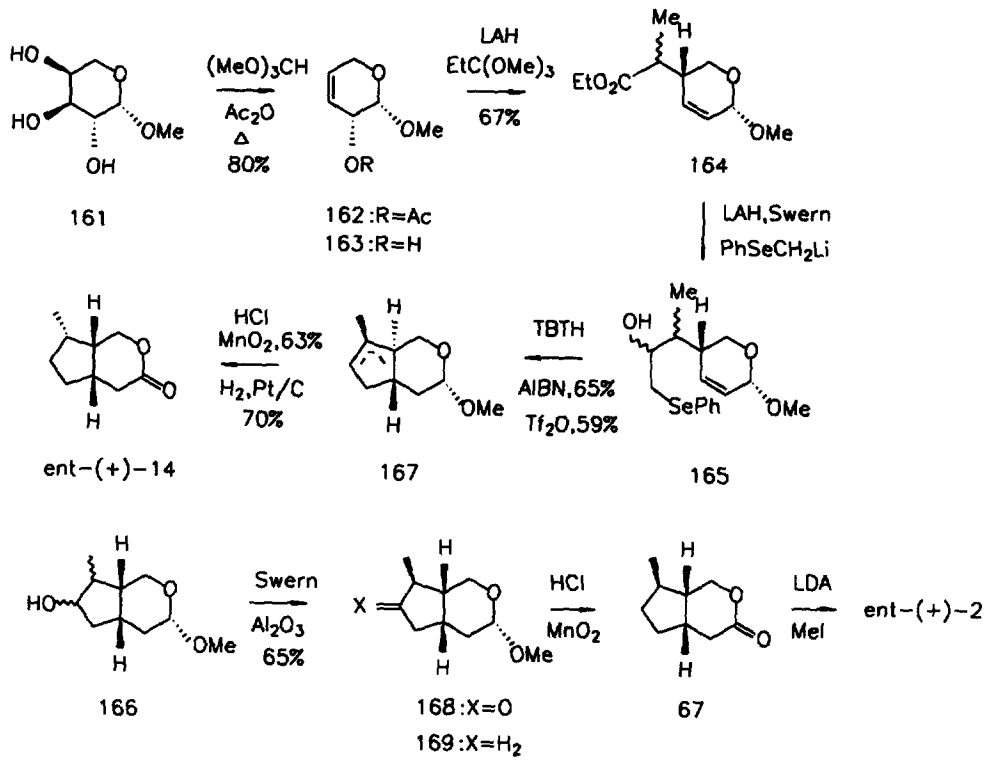
Reaction of bromide **158** under *n*-Bu_3SnH and AIBN conditions gave bicyclic products **159** as an undetermined mixture of isomers. The bulky trimethylsilylacetylene group was exploited to terminate the second cyclisation.[40] Protodesilylation of vinylsilane **159** with $PhSO_2H$ afforded a 70% yield of two diastereomers **160** in 3:1 ratio. Ozonolysis and equilibration gave the thermodynamically preferred *exo-exo* dimethyl ketone **91**, thereby confirming that the radical cyclisation had proceeded in agreement with Beckwith's rules.[41] The high *cis* selectivity at the ring junction and the excellent stereocontrol in the installation of the new C-Me stereocentre are noteworthy. The stereochemistry of the major bicyclic ketone **91** was confirmed by comparison of spectral data reported by Vandewalle[27b] and thus constituted a formal synthesis of *rac*-isoiridomyrmecin **2**.



Scheme 21: Kilburn synthesis of (±)-2

Methyl (+)-arabinoside **161** was orthoesterified, acetylated and finally pyrolysed to dihydropyran **162**. Deprotection of acetate **162** with LAH and Johnson's orthoester Claisen rearrangement ($EtC(OMe)_3$, CSA, 180°C) of the resultant allylic alcohol afforded ester **164** as an inseparable 1:1 mixture of epimers. Reduction of ester **164** to the aldehyde and exposure to phenylselenomethyllithium gave a diastereomeric mixture of hydroxy selenides **165** which was radical cyclised (*n*-Bu_3SnH, AIBN) to the bicyclic product **166**.[42] Dehydration of the reaction mixture gave a 3:2 mixture of olefins **167** in which the trisubstituted alkene isomer predominated. Oxidation of methyl acetal **167** to the unsaturated lactone and hydrogenation with Pt/C furnished a 92:8 mixture of *ent*-(+)-boschnialactone **14** and its C7-epimer **67**. A stereoselctive synthesis of the minor component **67** was accomplished through a modified route in which Swern oxidation of alcohol **166** and basic alumina promoted epimerisation afforded the *exo*-methyl cyclopentapyran **168** as the predominant isomer. The ketone **168** was reduced to the alcohol

and deoxygenated *via* the iodide to acetal **169**. Hydrolysis and oxidation yielded cyclopentapyranone **67** which was routinely homologated to *ent*-(+)-isoiridomyrmecin **2**.



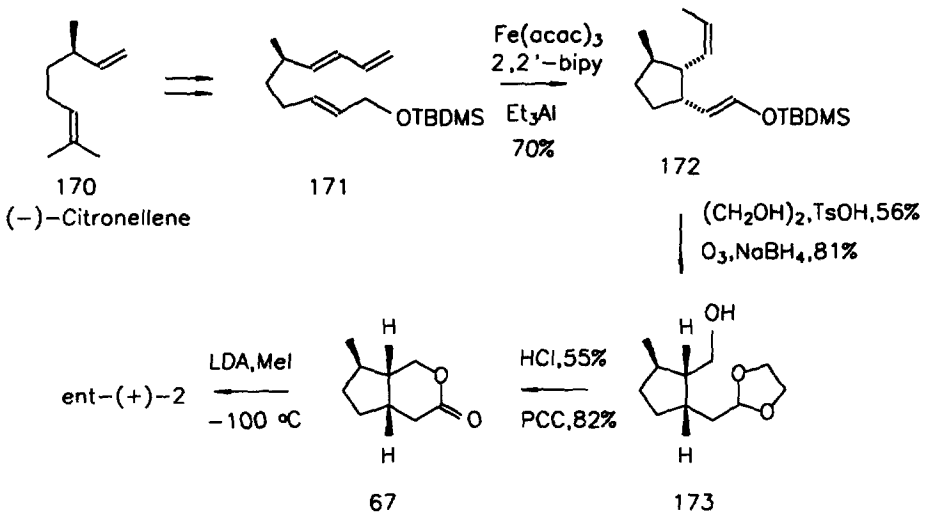
Scheme 22: Irie synthesis of ent-(+)-2 and ent-(+)-14

5.9 Organometallic reagents

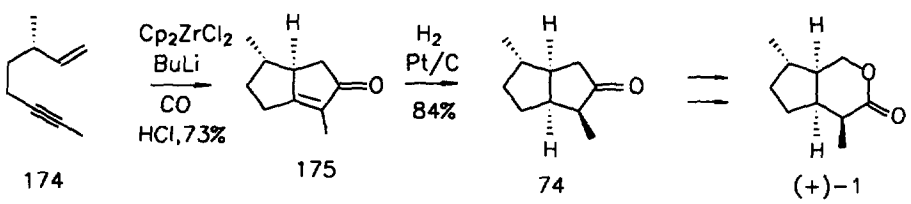
Two enantioselective approaches towards iridoid lactones mediated by organometallic reagents were reported in 1992. Takacs *et al.*[43] transformed *(R)*-(-)-citronellene to triene **171** through standard chemical manipulations of the two distinguishable double bonds in the starting chiron. Iron catalysed cyclisation of triene **171** afforded a mixture of geometrical silylenol ethers **172**; the 1,2-stereoinduction, guided by the methyl-bearing stereocentre, was excellent (~95% de). The crude enol ether **172** was acetalised, ozonised and reduced to hydroxy acetal **173** which readily cyclised to the lactol. Stereoselective (9:1) kinetic methylation of cyclopentapyranone **67** afforded *ent*-(+)-isoiridomyrmecin **2**.

Negishi and coworkers[44] converted the more reactive isopropenyl group of *(S)*-(+)-citronellene to the propyne group in **174**. The enyne **174** was treated with $ZrCp_2$ and the intermediate zirconabicyclic product subjected to carbonylation-protonolysis to produce bicyclic cyclopentenone **175** in ~90% de and 73% isolated yield.[45] The zirconium catalysed cyclisation was judged to be reversible and accordingly kinetic conditions (rt, 3h) gave a low de of ~50% whereas equilibration (rt, 18h) gave the above

mentioned de of ~90%. Catalytic hydrogenation of alkene **175** with Pt/C furnished predominantly product **74** (>98% de) through *exo* hydride delivery. The one-pot conversion of **74** to (+)-iridomyrmecin **1** was achieved following literature precedent.[24,27]



Scheme 23: Takacs synthesis of ent-(+)-2

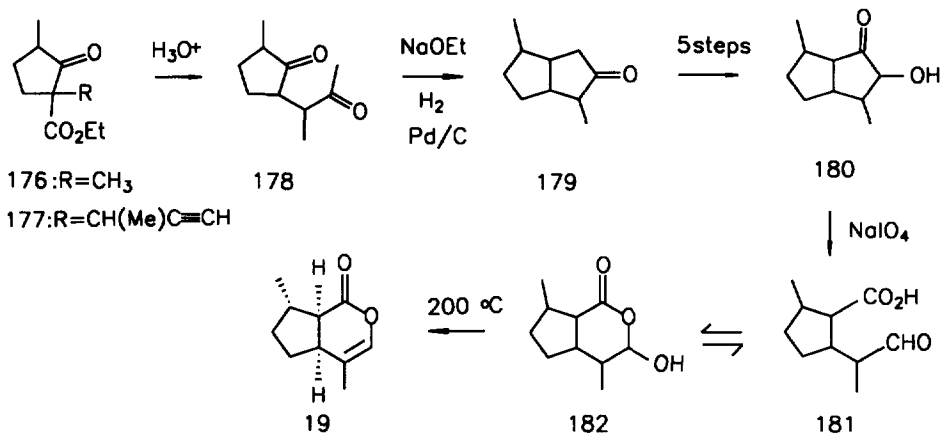


Scheme 24: Negishi synthesis of (+)-1

6. SYNTHESIS OF TYPE-II IRIDOID LACTONES

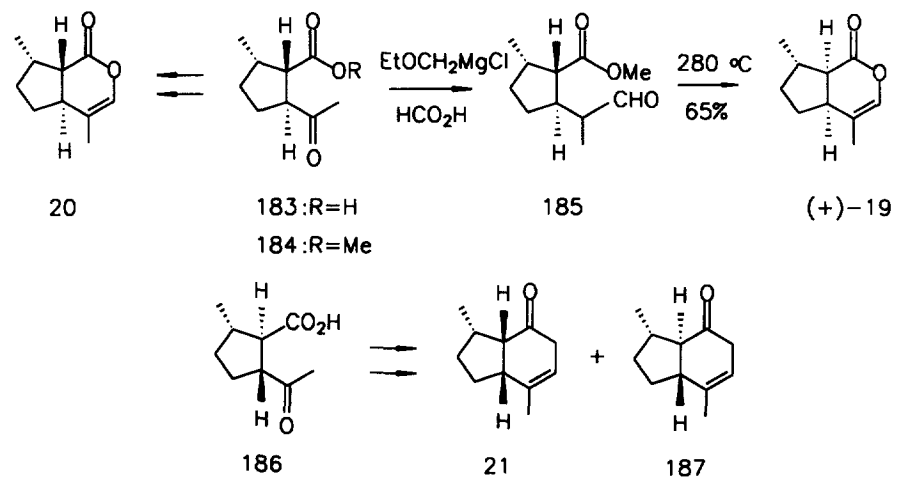
6.1 The early syntheses

The first synthesis of *dl*-nepetalactone **19** was reported in 1960 by Sakan and coworkers.[46] Ethyl 3-methyl-2-oxocyclopentanecarboxylate **176** was alkylated with 3-bromobutyne to **177** and the acetylene group hydrolysed to diketone **178**. Intramolecular condensation of the γ-diketone gave the expected cyclopentenone which was hydrogenated to stereorandom bicyclo[3.3.0]octanone **179**. Transformation of ketone **179** to the unstable α-ketol **180** and oxidation with periodate afforded aldehyde acid **181** in equilibrium with its lactol **182**. Pyrolytic dehydration of the lactol gave *rac*-nepetalactone **19** in undetermined yield.



Scheme 25: Sakan synthesis of rac-19

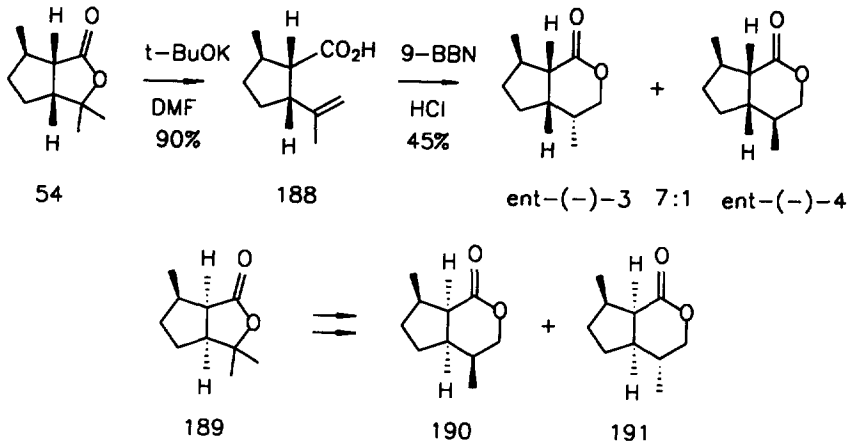
Nepetalactone **19** and its three other stereoisomers were synthesised from nepetonic acids (+)-*trans-syn* **183** and (-)-*trans-anti* **186**.[47] The methyl ester **184** was homologated to aldehyde acid **185**, whose epimerisation and cyclisation at 280°C gave (+)-*cis-anti*-nepetalactone **19**, the active constituent of cat-nip oil. The other three nepetalactone diastereomers, *trans-syn*-epinepetalactone **20**, *cis-syn*-**21** and *trans-anti*-**187** were synthesised using related methodology.



Scheme 26: Trave synthesis of (+)-19

This was followed by the synthesis of four of the eight possible stereoisomers of dihydronepetalactones.[48] The ring opening of *cis-anti*-pulegenolide **54** with *t*-BuOK in hot DMF yielded *cis-anti*-2-isopropenyl-5-methyl-1-cyclopentanecarboxylic acid **188** (90%). Hydroboration-oxidation of alkene **188** and lactonisation afforded a 7:1 mixture of *ent*-(-)-dihydronepetalactone **3** and *ent*-(-)-isodihydronepetalactone **4**. Similarly, *cis-syn*-pulegenolide **189** produced a 5:1 ratio of *cis-syn*-

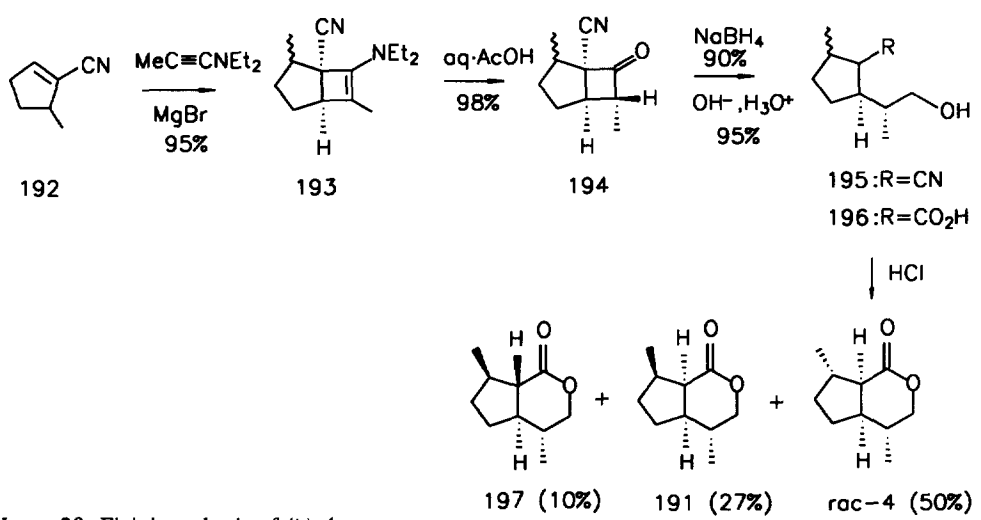
dihydronepetalactone **190** and *cis-syn*-isodihydronepetalactone **191**. The dihydronepetalactones are known to be more attractive to cats than nepatalactones.



Scheme 27: Wolinsky synthesis of ent-(-)-3 and ent-(-)-4

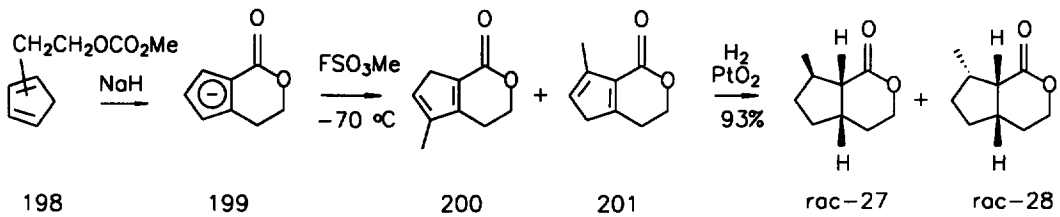
6.2 Stereoselective C-C and C-H bond formation

Magnesium bromide catalysed Michael addition of diethylaminopropyne to 5-methyl-1-cyanocyclopentene **192** afforded a zwitterionic intermediate which cyclised to cyclobutene **193**.[49] Hydrolysis of enamine **193** to cyclobutanone **194** and retro-aldol reaction of the hydroxy nitrile afforded cyclopentane **195** as a mixture of diastereomers at the C-Me and C-CN centres. Hydrolysis of the nitrile to acid **196** and lactonisation afforded a mixture of *rac*-isodihydronepetalactone **4** (50%), *cis-syn*-isodihydronepetalactone **191** (27%) and *trans-anti*-isodihydronepetalactone **197** (10%).



Scheme 28: Ficini synthesis of (±)-4

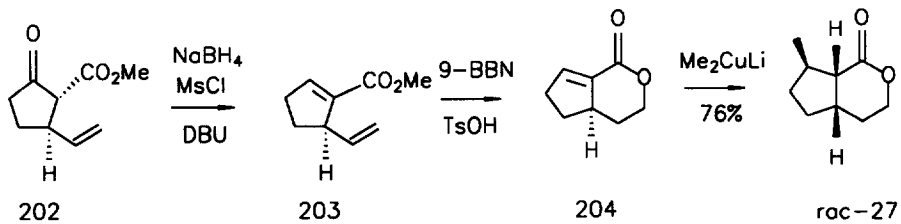
Deprotonation of cyclopentadienylethyl methyl carbonate **198** with NaH gave the corresponding cyclopentadienyl anion which underwent intramolecular attack on the carbonate group to produce anion **199**. Methylation of **199** with methyl fluorosulfonate at -70°C gave a mixture of regioisomers **200** (17%) and **201** (50%). Hydrogenation of the major isomer **201** with Pt catalyst resulted in the formation of nine carbon iridoids *rac*-mitsugashiwalactone **27** and *rac*-onikulactone **28** (1.8:1.0) in quantitative yield.[50]



Scheme 29: Fujisawa synthesis of (±)-27 and (±)-28

Nugent and Hobbs[51] carried out the tandem conjugate addition and cyclisation of vinyl cuprate with dimethyl 2-hexene-1,6-dicarboxylate to obtain a 94:6 ratio of diastereomers **202** (80%), in which the *trans* isomer predominated. Borohydride reduction and elimination gave 2-carbomethoxy-3-vinylcyclopentene **203**. Selective hydroboration-oxidation of the isolated, reactive alkene of **203** gave the corresponding hydroxy ester which was cyclised to lactone **204**. Conjugate methyl cuprate addition to unsaturated lactone **204** afforded *rac*-mitsugashiwalactone **27** in >95% stereoisomeric purity and 76% isolated yield.

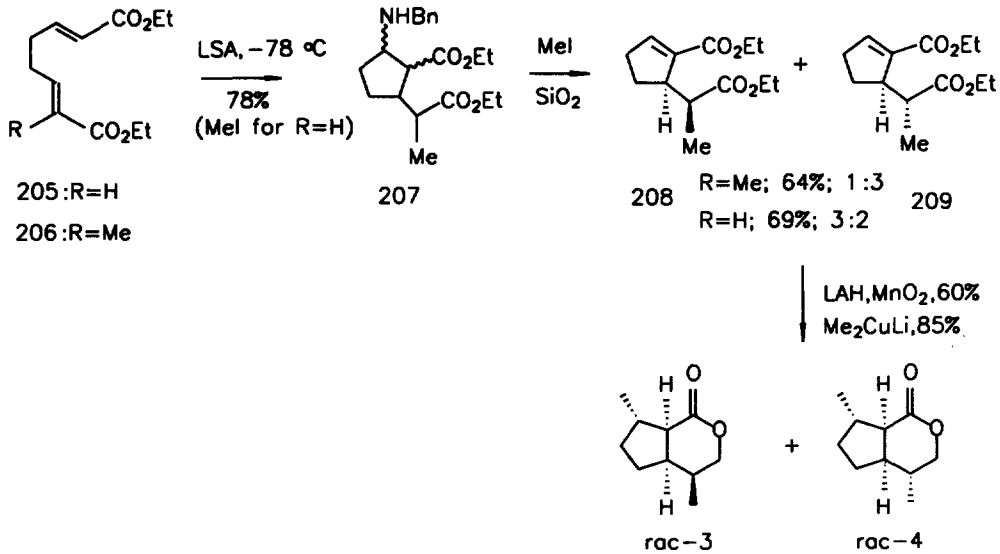
Amri *et al.*[52] synthesised the unsaturated lactone **204** by a different route employing a S_N2' coupling between ethyl 5-acetoxy-1-cyclopentenecarboxylate and $LiCH_2CO_2Bu^t$, and completed the synthesis of *rac*-mitsugashiwalactone **27** by a methyl cuprate addition.



Scheme 30: Nugent synthesis of (±)-27

Treatment of unsymmetrical diester **206** with lithium *N*-benzyltrimethylsilylamide (LSA) afforded a diastereomeric mixture of cyclised product **207** through tandem conjugate additions on the dioic ester. This mixture was converted to a 1:3 mixture of cyclopentenes **208** and **209** in 64% yield upon elimination of the dialkylamino group.[53] On the other hand, a 3:2 ratio of esters **208** and **209** was obtained in 69% yield when the tandem sequence was carried out on diester **205** and the methyl group introduced by quenching the enolate of the cyclopentene ester with MeI. The esters **208** and **209** were independently

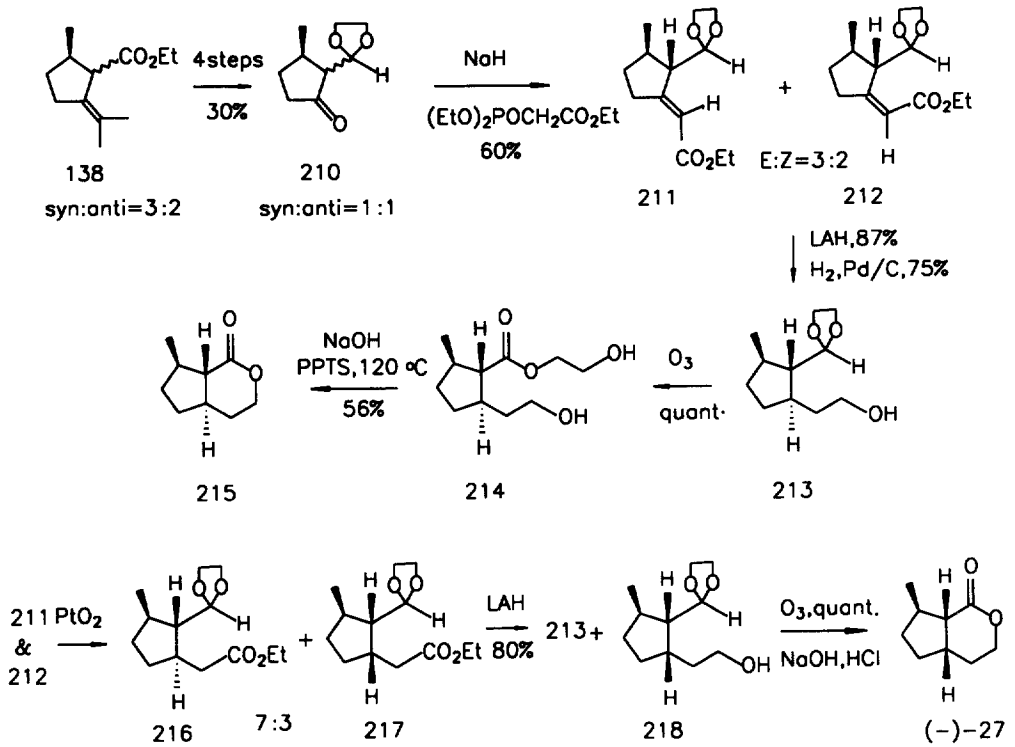
transformed into *rac*-dihydronepetalactone **3** and *rac*-isodihydronepetalactone **4**, respectively, using the Amri[52] sequence (LAH, MnO_2, Me_2CuLi).



***Scheme 31:** Uyehara synthesis of (±)-3 and (±)-4*

A 1:1 mixture of β-keto acetal **210** was prepared from a 3:2 mixture of *syn/anti* esters **138** in 30% overall yield through routine chemical transformations. Horner condensation of ketone **210** with diethylphosphonoacetic acid afforded a 2:3 mixture of *Z*- and *E*-unsaturated esters **211** and **212**, with concomitant epimerisation to the more stable *anti* orientation of methyl and acetal groups. Reduction of unsaturated esters **211**,**212** and hydrogenation of the allylic alcohol with Pd/C afforded the unexpected *trans* stereoisomer **213** exclusively. The hydrogenation takes place *syn* to the polar acetal group, presumably assisted by chelation of acetal oxygen atoms to the palladium surface, to produce the undesired *trans* relationship at C4a-C7a. Ethylene acetal **213** was ozonised to ester **214**,[54] hydrolysed to the hydroxy acid and finally lactonised to yield *trans*-fused type-II lactone (-)-epimitsugashiwalactone **215**.[8]

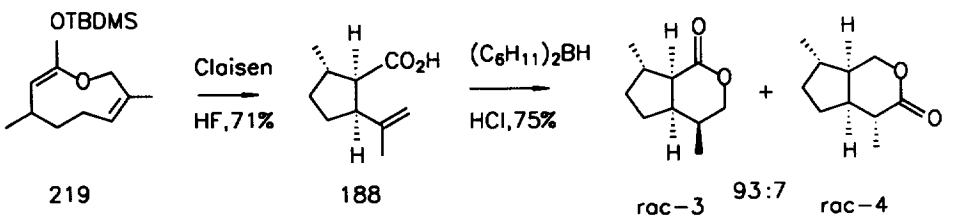
In order to complete the synthesis of mitsugashiwalactone **27**,[8] the unsaturated esters **211** and **212** were hydrogenated with Pt/C catalyst to provide a 3:7 mixture of the desired *cis*-ester **217** and *trans*-isomer **216**, which were reduced as such to hydroxy acetals **213** and **218**. Saponification of the inseparable mixture of esters and then acidification at ambient temperature furnished the *cis*-lactone **27** readily; the *trans*-hydroxy acid remained unreacted since it cyclises at 100°C. Chromatographic purification afforded natural (-)-mitsugashiwalactone **27** in enantiomeric purity superior to that reported previously.[43]



Scheme 32: Nangia synthesis of (-)-27

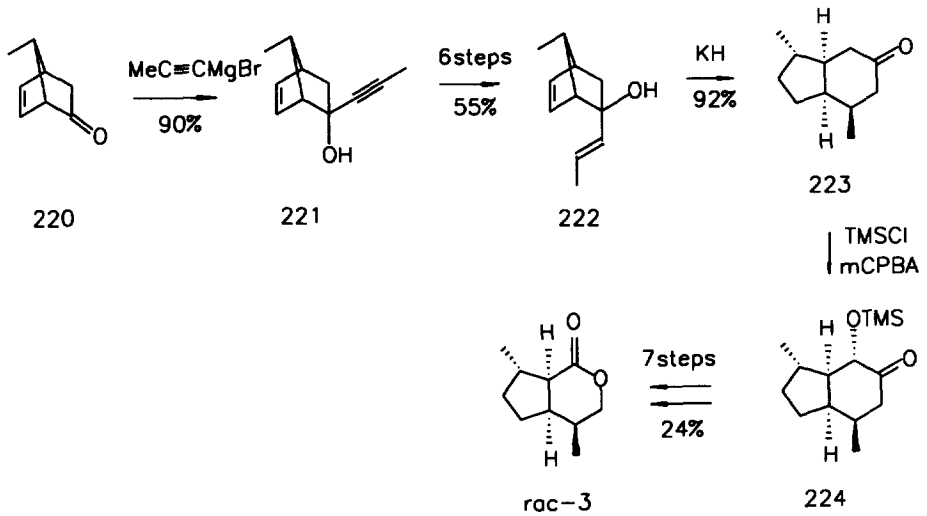
6.3 Sigmatropic rearrangements

The silyl ketene acetal **219** was rearranged to the silyl ester and hydrolysed to acid **188**.[55] The highly selective (>98%) formation of the *cis-anti*-cyclopentane carboxylic acid **188** is attributed to the absence of serious $A^{(1,3)}$ type interaction[35] between the endocyclic oxygen atom and the pseudoaxial methyl group in the favoured boat-like conformer. Stereoselective hydroboration of **188** and cyclisation[48] directly provided the cat-nip oil components *rac*-dihydronepetalactone **3** and *rac*-isodihydronepetalactone **4** in 93:7 ratio (75%). Alternatively, acid **188** was easily converted to acetate **56**, which has already been parlayed to iridomyrmecin **1**.[22]



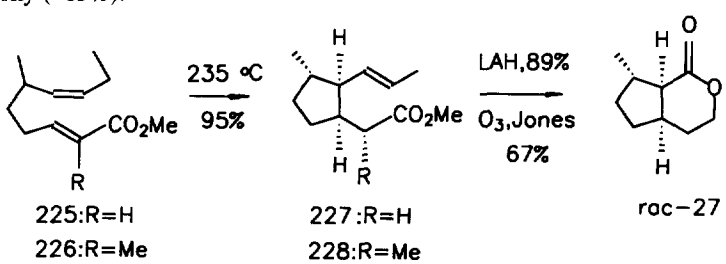
Scheme 33: Funk synthesis of (±)-3 and (±)-4

Norbornenone **220** was treated with propynyl Grignard to afford predominantly the *exo* addition product **221** (90%) which was rearranged to the desired *exo* alcohol **222** *via* allylsilane chemistry.[56] The *anti* selective reaction of allylsilane combined with preferential *exo* attack by electrophile installed the *trans*-propenyl group *endo* on the norbornene ring. The anionic oxy-Cope rearrangement (KH) of *exo*-alcohol **222** afforded a single bicyclo[4.2.0]ketone **223** in which the four stereogenic centres were correctly disposed. The remaining steps to extrude the ketonic carbon *via* silyloxy ketone **224** were conventional functional group conversions and afforded *rac*-dihydronepetalactone **3** in 24% yield.



Scheme 34: Fleming synthesis of (±)-3

Thermal ene-cyclisation of the α,ω-diene **225** at 235°C gave stereoselectively the *cis*-fused functionalised cyclopentane **227**.[57] LAH reduction of ester, oxidative cleavage of the alkene, and Jones oxidation gave *rac*-mitsugashiwalactone **27** in >97% stereopurity. In addition, the homologous ene product **228** was elaborated to *rac*-isoiridomyrmecin **2** and *rac*-isodihydronepetalactone **4** in lower stereochemical purity (~85%).

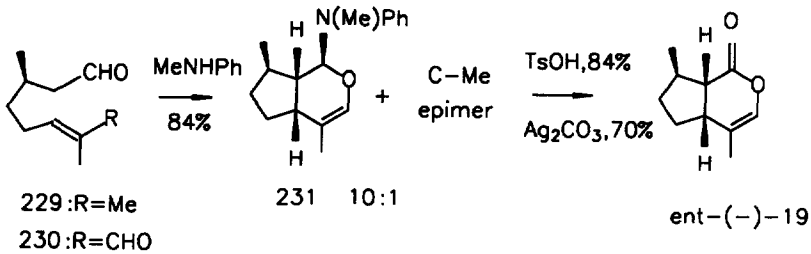


Scheme 35: Mikami synthesis of (±)-27

6.4 [4+2] and [2+2] cycloadditions

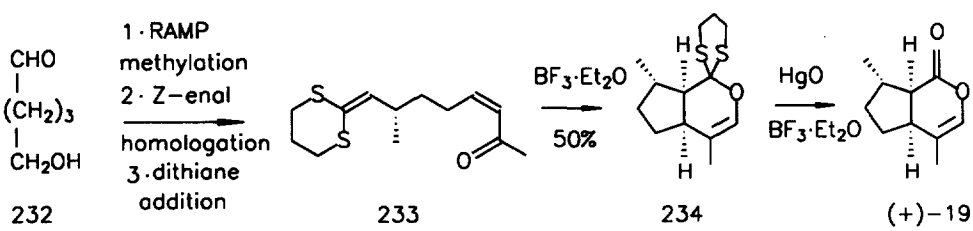
Enantioselective syntheses of (-)- and (+)-nepetalactone through a hetero Diels-Alder approach were independently published in successive papers by Schreiber[58] and Denmark.[59] The dialdehyde

230 of *(R)*-citronellal was reacted with with *N*-methylaniline. The intramolecular cycloaddition of aldehyde enamine with enal (rt, 30 min) provided a separable 10:1 mixture of the desired dihydropyran **231** and its methyl epimer in 84% yield. Equilibration (10 h) furnished a better 25:1 ratio of diastereomers, although in lower yields (60-65%). The dihydropyran **231** was hydrolysed to unsaturated lactol whose Fetizon oxidation with Ag_2CO_3 afforded *ent*-(-)-nepetalactone **19**.[58]



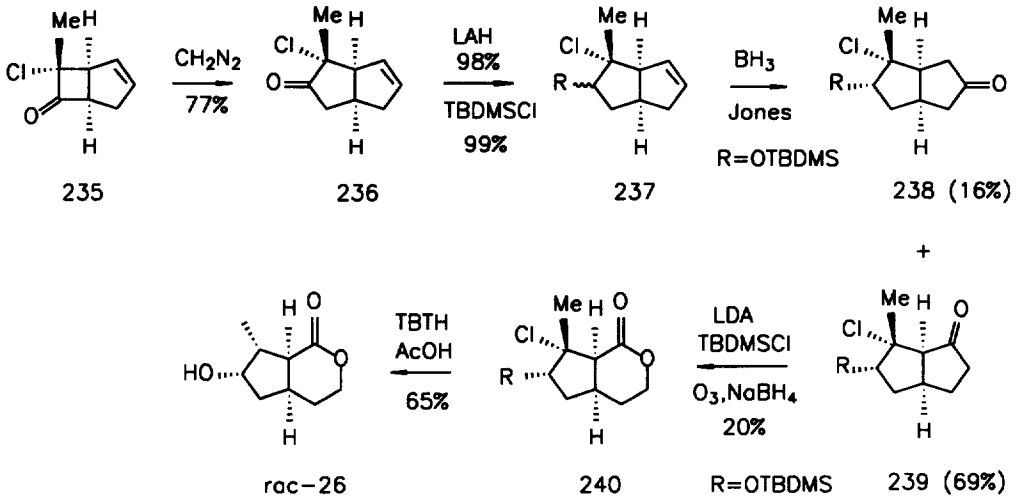
Scheme 36: Schreiber synthesis of ent-(-)19

5-Hydroxypentanal was homologated to introduce the stereodirecting methyl group using an asymmetric alkylation on the RAMP hydrazone.[60] The aldehyde was homologated to the desired *(Z)*-enal and converted to the ketene thioacetal (+)-**233** in 96% ee. Exposure of *(Z)*-enal **233** to $BF_3.Et_2O$ catalysed cyclisation produced exclusively the dithioortholactone **234** bearing the three correct absolute stereocentres. Mercuric oxide assisted hydrolysis of dithioacetal **234** afforded (+)-nepetalactone **19** in 76% yield.[59]



Scheme 37: Denmark synthesis of (+)-19

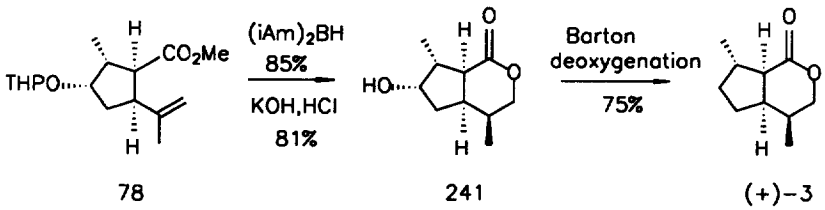
The C6-hydroxylated monoterpene lactone boonein **26** is of great biogenetic interest but only one total synthesis of this compound is reported.[61] The major stereo- and regioisomer **235** of the [2+2] cycloaddition of cyclopentadiene and methylchloroketene was ring-expanded with diazomethane to the bicyclo[3.3.0]octenone **236** in 77% yield. Reduction of the ketone with LAH gave a 1.8:1.0 ratio of diastereomeric alcohols **237** in quantitative yield. The major TBDMS ether was hydroborated and oxidised to ketones **238** (16%) and **239** (69%). The O-silylated enol ether of ketone **239** was ozonised and reduced to give the desired δ-lactone **240**. Hydride delivery from the convex face of the molecule and desilylation furnished *rac*-boonein **26**.



Scheme 38: Lee synthesis of (±)-26

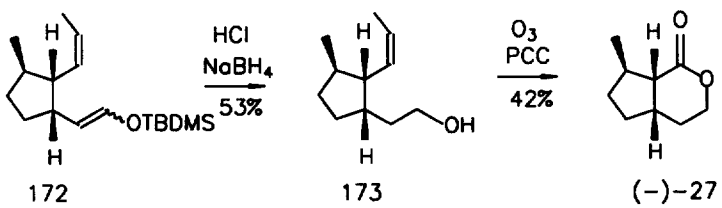
6.5 Elaboration from type-I intermediate

Lee[25] and Takacs[43] were successful in exploiting an advanced intermediate to expeditiously target both types of lactones. The Favorskii rearrangement product **78** was elaborated to hydroxy ester by hydroboration-oxidation; saponification of the ester and acid promoted lactonisation-cum-deprotection afforded 6-hydroxy lactone **241**. Radical deoxygenation of alcohol **241** yielded the first synthetic sample of natural (+)-dihydronepetalactone **3**.[25]



Scheme 39: Lee synthesis of (+)-3

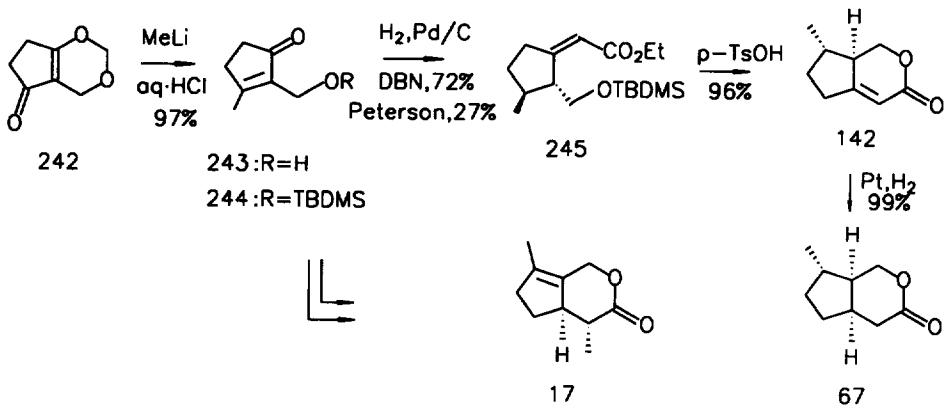
Silyl enol ether **172** was hydrolysed and reduced to alcohol **173** in 53% yield. Ozonolysis of hydroxy alkene **173** to the lactol and PCC oxidation afforded synthetic (-)-mitsugashiwalactone **27** in 42% yield.[43]



Scheme 40: Takacs synthesis of (-)-27

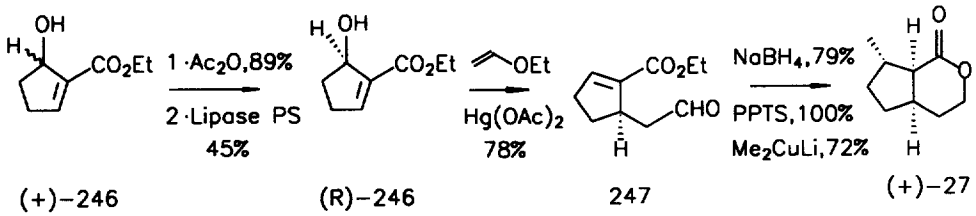
Note added: We became aware of two recent papers after submission of the manuscript.

Ohba *et al.*[62] synthesised cyclopentenone **243** by methylative 1,3-carbonyl transposition of dioxinone **242**. Hydrogenation, epimerisation and olefination of silyl ether **244** afforded *Z*-ester **245** which was cyclised under acidic conditions to the known lactone **142**. Stereoselective hydrogenation of **142** provided cyclopentapyranone **67**, the penultimate precursor to iridoids *rac*-**1**, *rac*-**2** and *rac*-**13**. Cyclopentenone **244** was also elaborated to *rac*-isodehydroiridomyrmecin **17**.



Scheme 41: Ohba synthesis of (±)-1, (±)-2, (±)-13 and (±)-17

Ogasawara and coworkers[63] obtained alcohol *(R)*-**246** in 99% ee by lipase catalysed hydrolysis of the racemic acetate. Claisen rearrangement on the ethyl vinyl ether derived from allylic alcohol *(R)*-**246** afforded γ,δ-unsaturated aldehyde **247** with complete retention of chiral integrity. Reduction of the aldehyde, cyclisation to lactone and methyl cuprate addition furnished *ent*-(+)-mitsugashiwalactone **27**.



Scheme 42: Ogasawara synthesis of (+)-27

7. CONCLUSIONS

Since the discovery of naturally occurring iridoid monoterpene lactones in the 1950s, numerous research papers have been published on their synthesis in the last four decades. The stereoselective synthesis of iridoid lactones has been carried out very successfully with ee and de values in excess of 95%. Out of the 40 or so papers published to date, about 25 papers describe the synthesis of type-I iridoids and the remaining deal with the synthesis of type-II lactones. A limitation of most routes is that

they target either lactones in the type-I category or in the type-II category, but very rarely natural products of both types through a common advanced intermediate. The flexibility to synthesise both types of regioisomeric iridoids is inherent in only four synthetic approaches published from the laboratories of Wolinsky,[22,48] Lee,[25] Takacs,[43] and our group.[8,36]

A large number of stereoselective carbon-carbon bond forming reactions[64] have been utilised for correctly installing the contiguous stereogenic centres on the iridane skeleton. The control of relative as well as absolute stereochemistry is indeed remarkable in the efforts to date. However, approaches based on enzyme catalysed biotransformations[65] for the synthesis of carbocyclic skeletons are conspicuously absent in the literature on iridoids. This gap should serve as a challenge for future research on the synthesis of iridoids and other classes of complex natural products.

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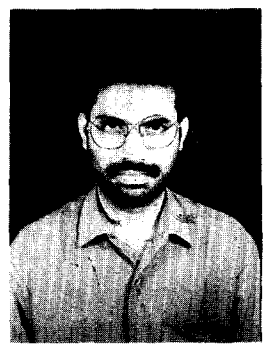

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